CENTER FOR MOLECULAR MODELING

Computational microscopy of membrane proteins: methods and tools

Ahmad Reza Mehdipour

Center for Molecular Modeling

Ghent University

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GHENT UNIVERSITY

FACULTY OF ENGINEERING AND ARCHITECTURE

Outline

- Theoretical Biophysics
- Molecular dynamics (MD) simulations
- Applications of MD simulations in membrane biology
  - Protein-lipid interaction: lipid flippase
- Advanced methods
- Future directions

Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World

Macroscopic World

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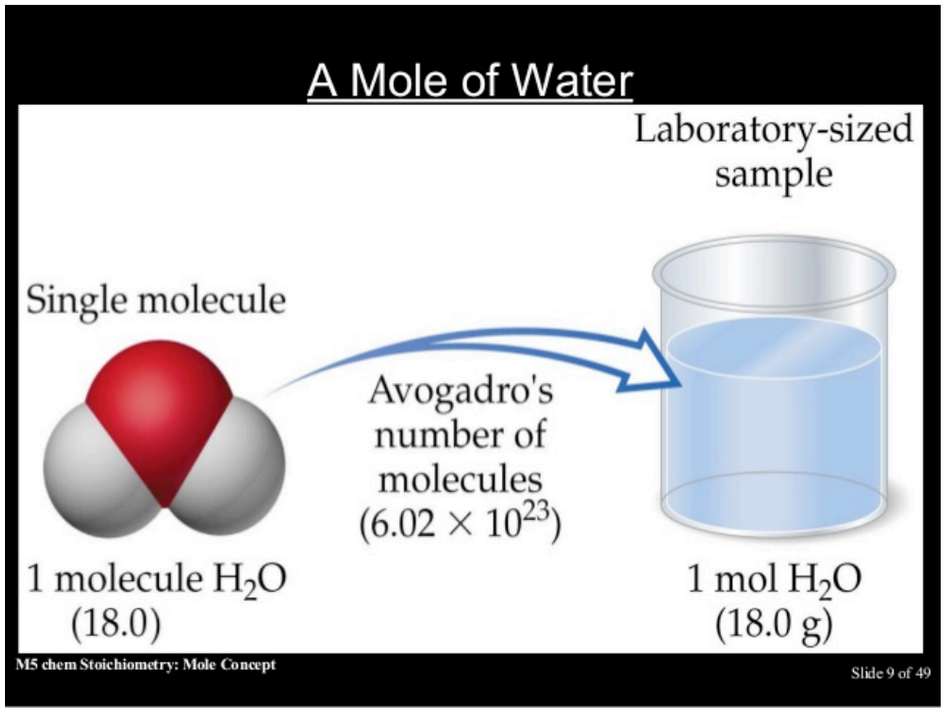
Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World

Macroscopic World



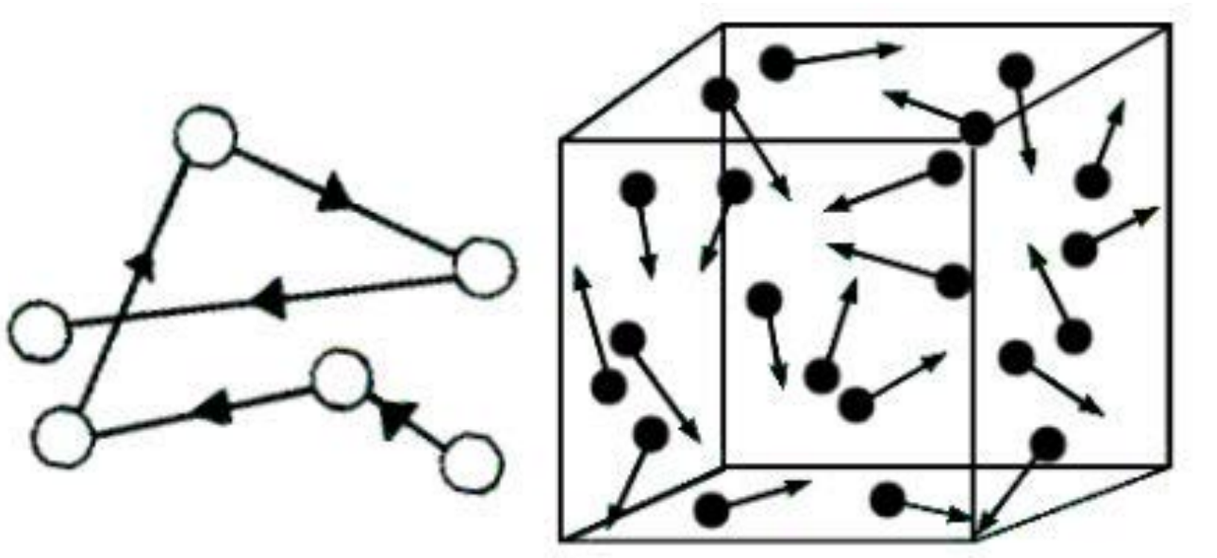
http://chemistry.tutorvista.com/

Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World

Macroscopic World

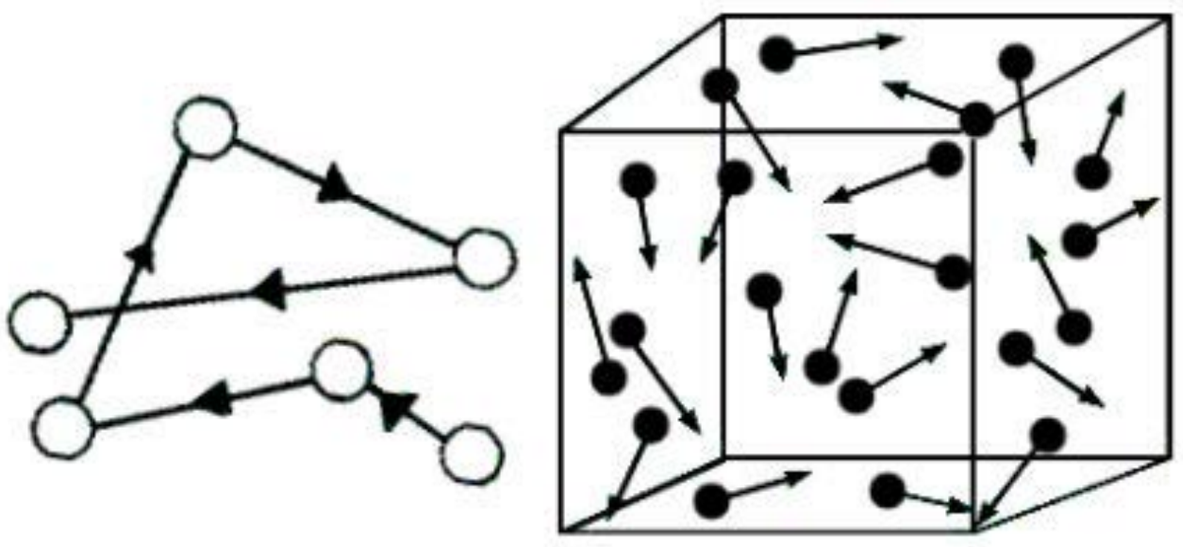


Stochastic Process

Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World



Stochastic Process

Macroscopic World

Pressure

Volume

Theoretical Biophysics

Microscopic World ⟷ Macroscopic World

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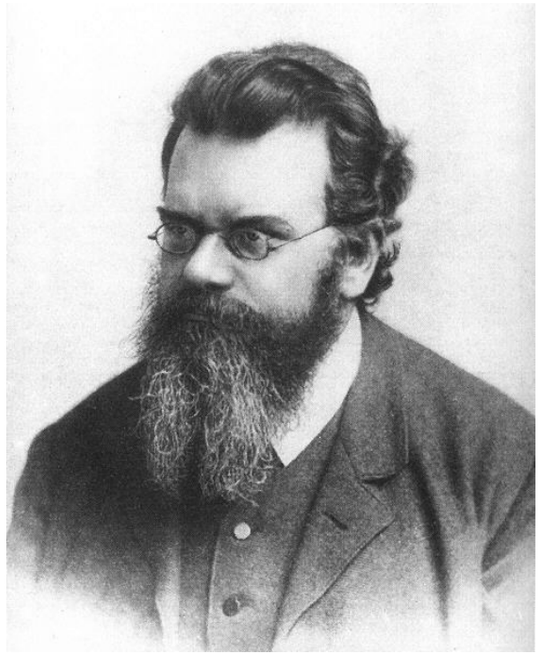
Theoretical Biophysics

Microscopic World ⟷ Macroscopic World



Ludwig Boltzmann

Founder of statistical mechanic/physics

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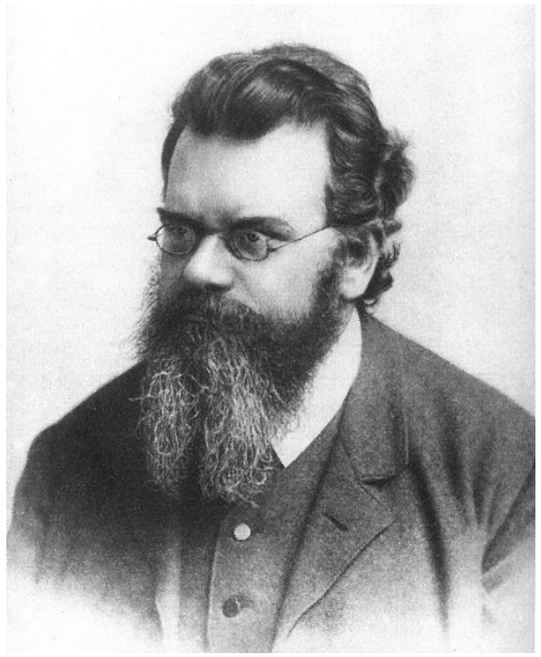
Theoretical Biophysics

Simple systems

Microscopic World ⟷ Macroscopic World

Analytical solutions



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Theoretical Biophysics

Microscopic World ⟷ Macroscopic World

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Theoretical Biophysics

But for complex systems???

Microscopic World ⟷ Macroscopic World

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Theoretical Biophysics

But for complex systems???

Microscopic World ⟷ Macroscopic World

Numerical solutions

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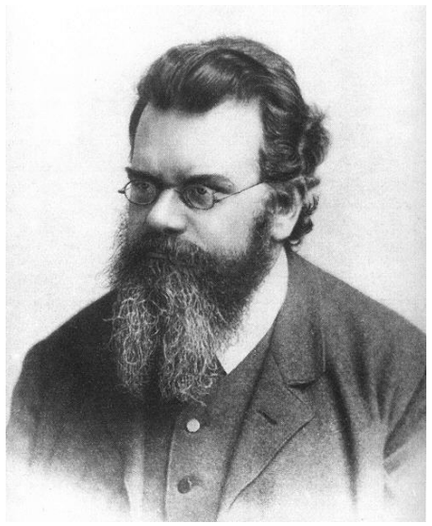
Theoretical Biophysics

But for complex systems???

Microscopic World ⟷ Macroscopic World

Numerical solutions



Ludwig Boltzmann

Founder of Statistical Physics

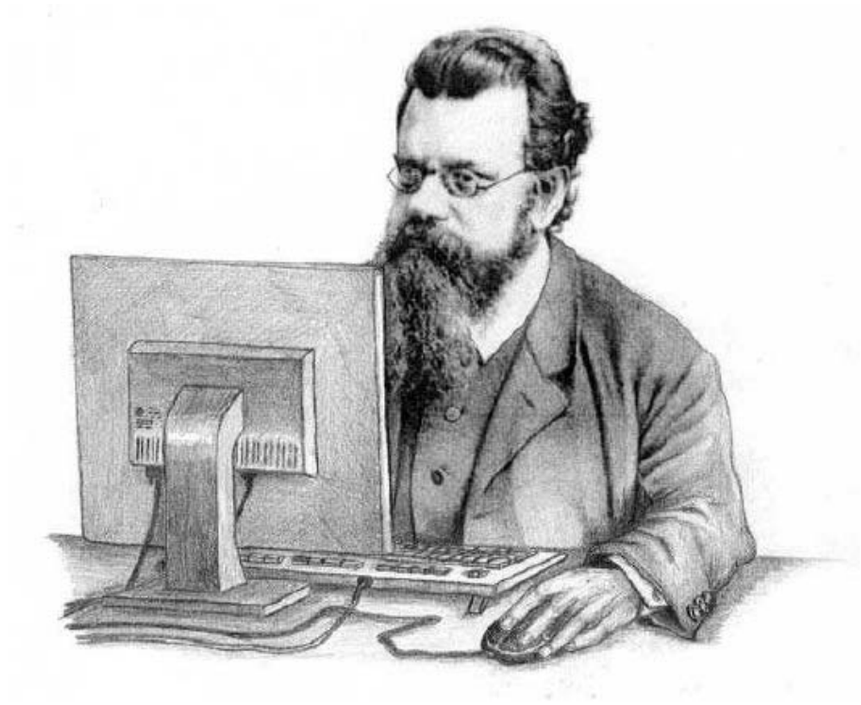


Figure 1. Boltzmann at work (Drawing by Bernhard Reischl, University of Vienna).

Ludwig Boltzmann, in 21st centry

Methods overview

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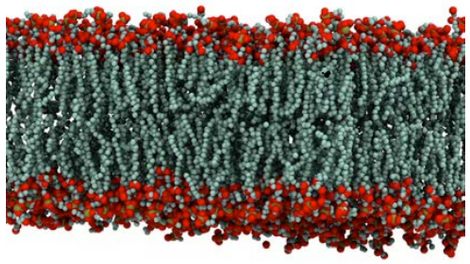
Methods overview

Molecular dynamics simulation



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Methods overview

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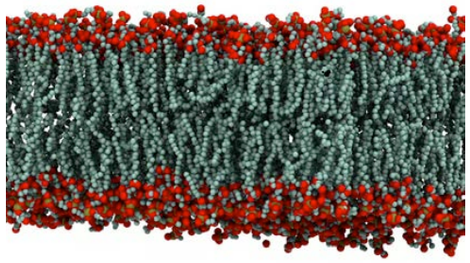

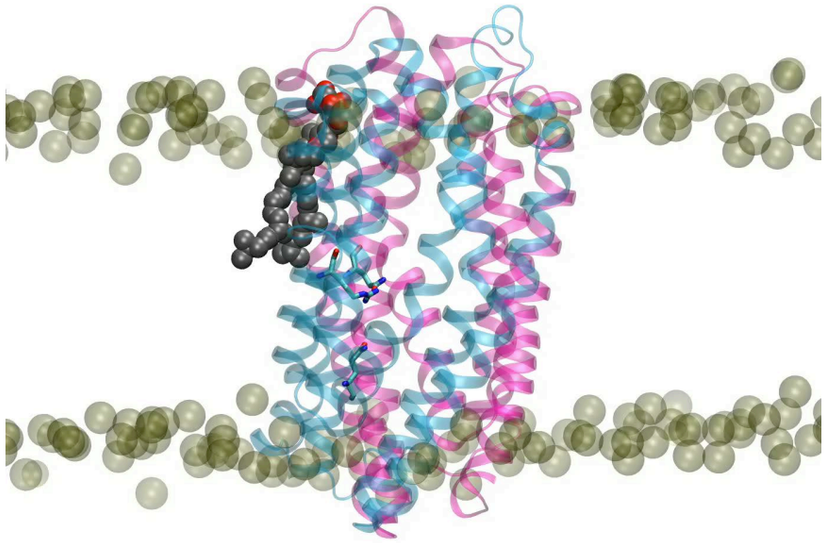

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Methods overview

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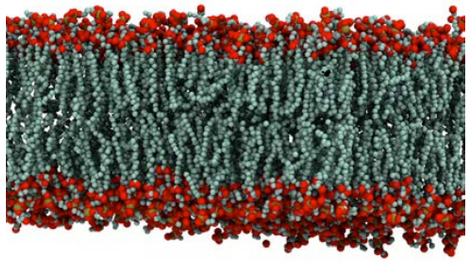
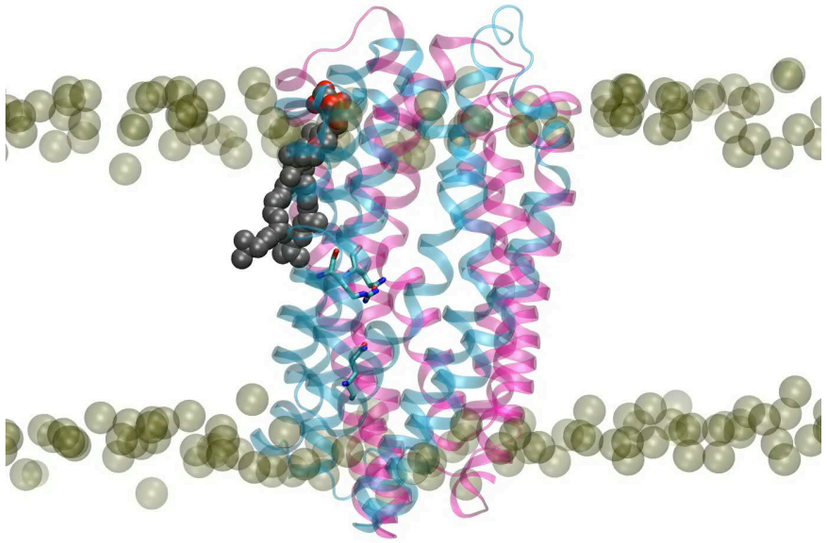
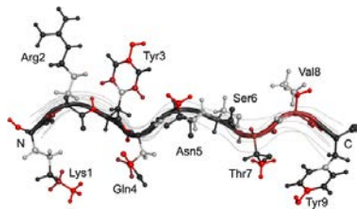
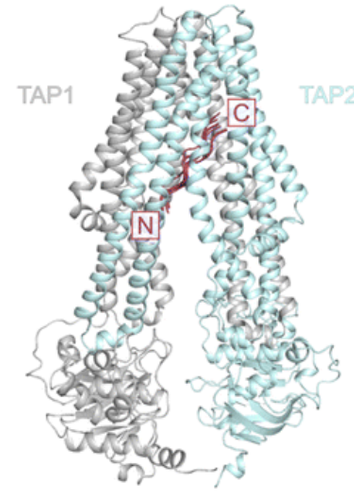




Molecular docking





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Methods overview

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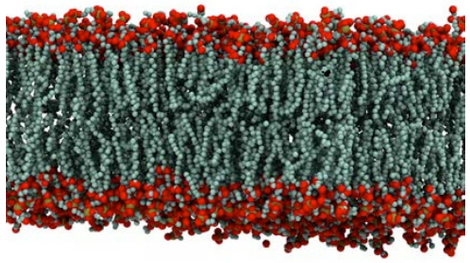

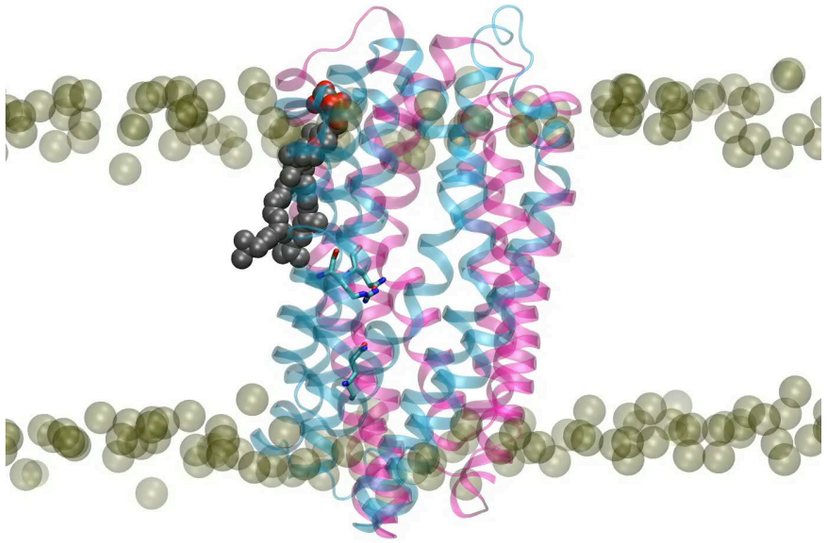

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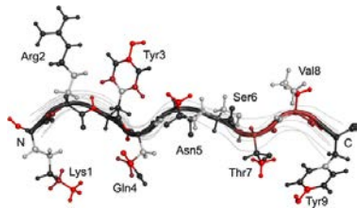

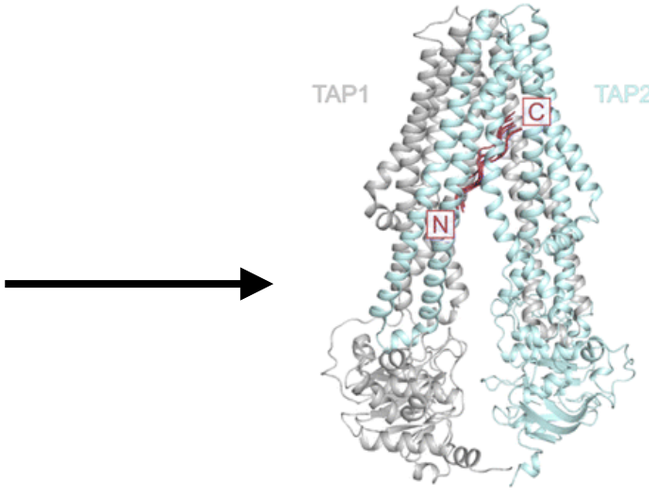

Integrative modeling

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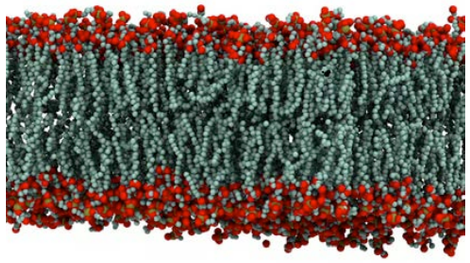
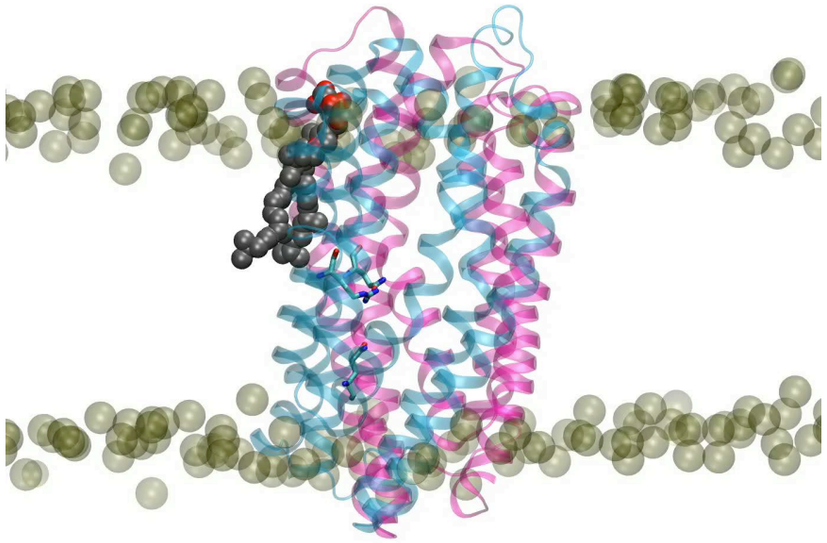
Methods overview

Molecular dynamics simulation





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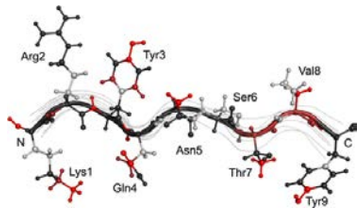
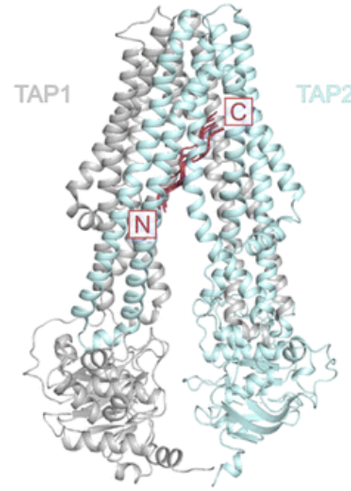
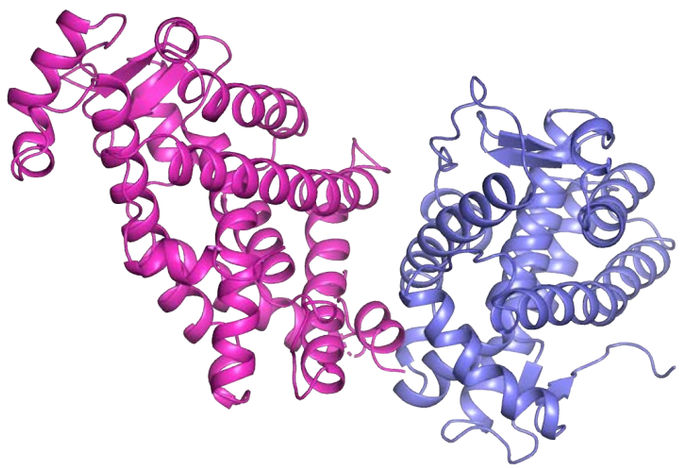




Integrative modeling

Structural bioinformatics



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Methods overview

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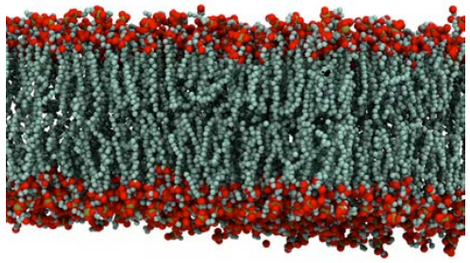

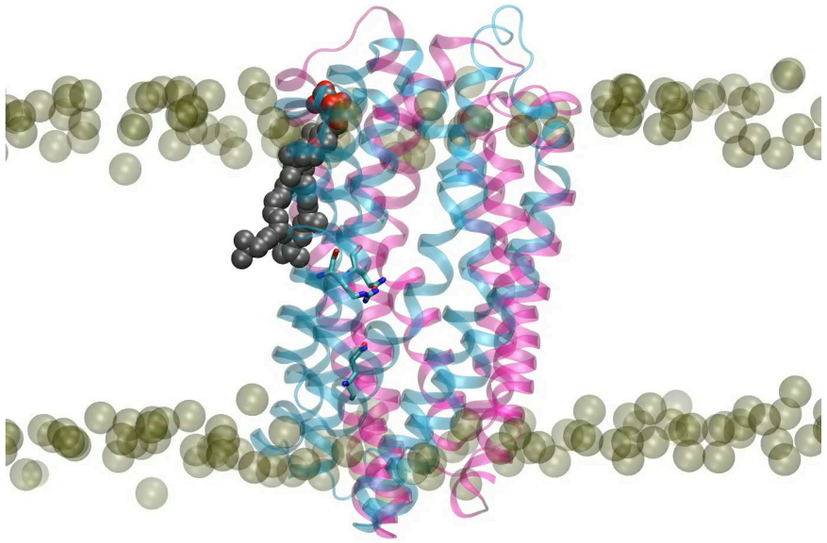

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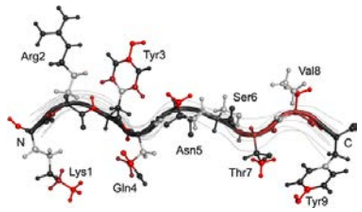

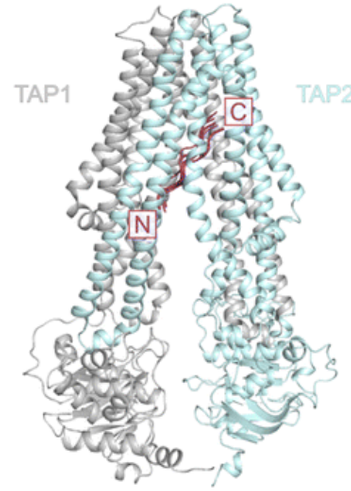

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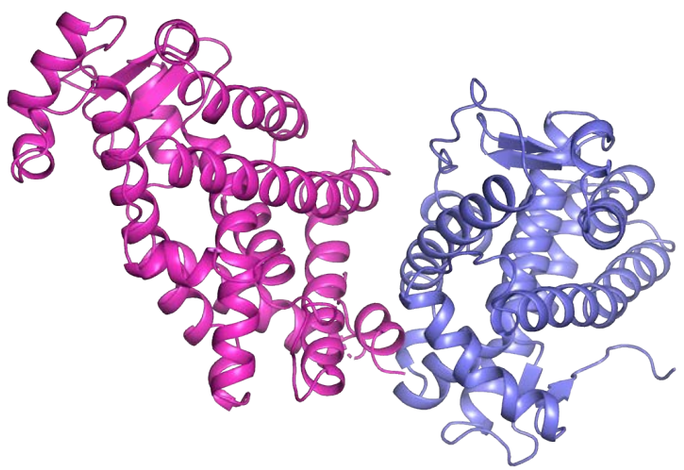

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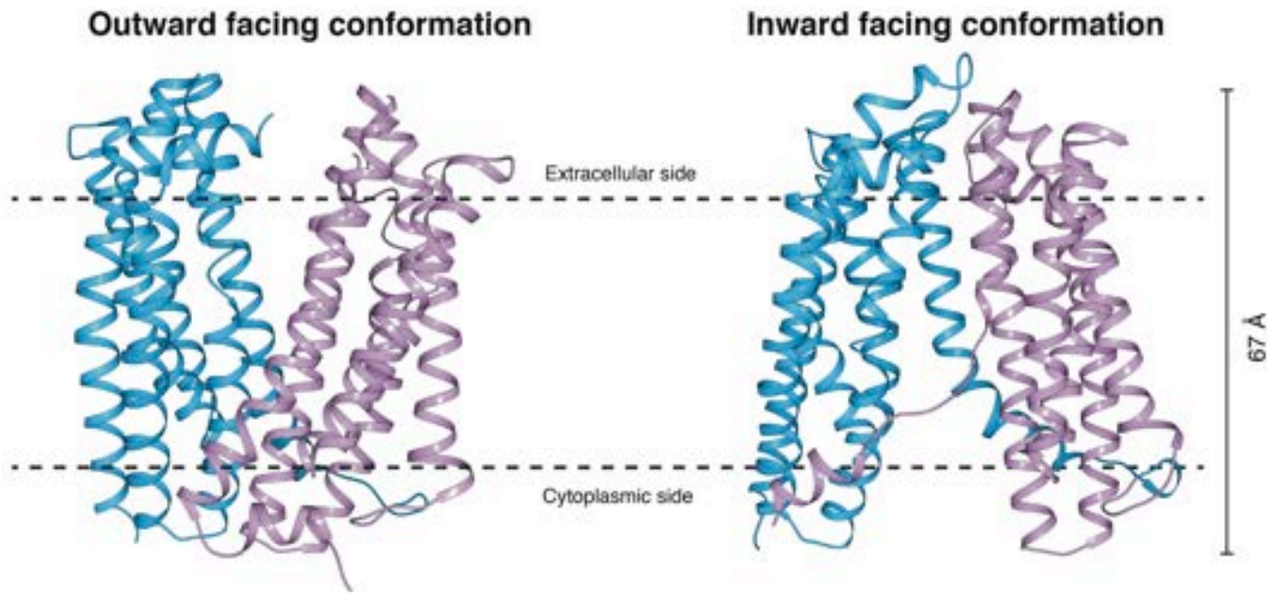
Structures are snapshots

Structural information
Static



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Structural information
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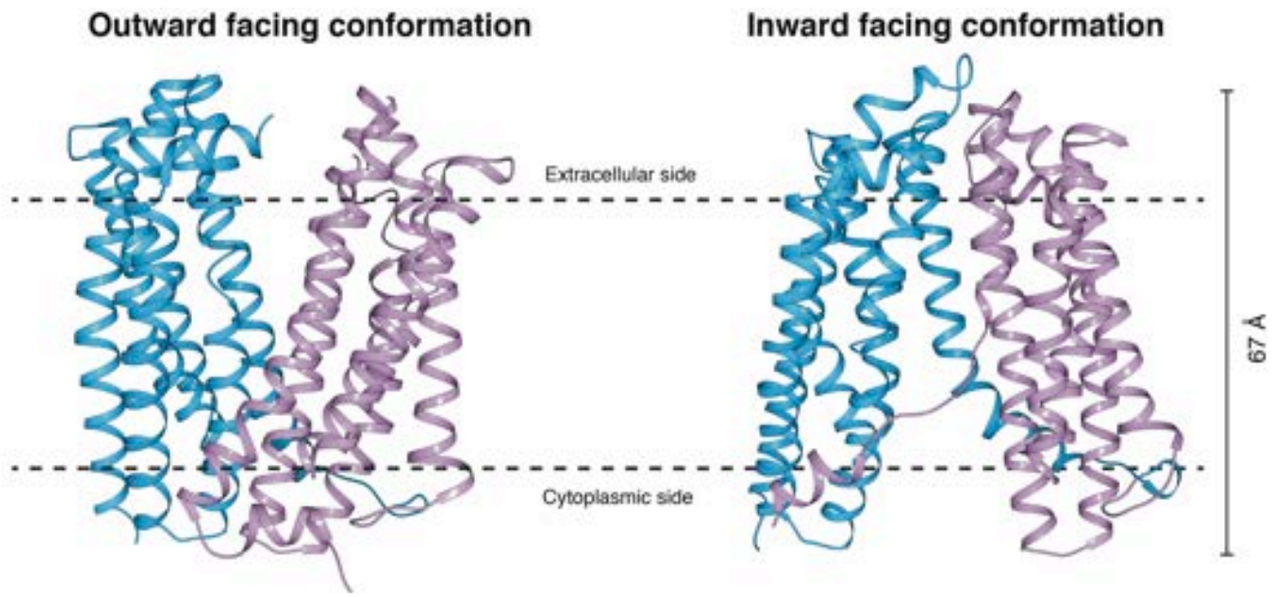
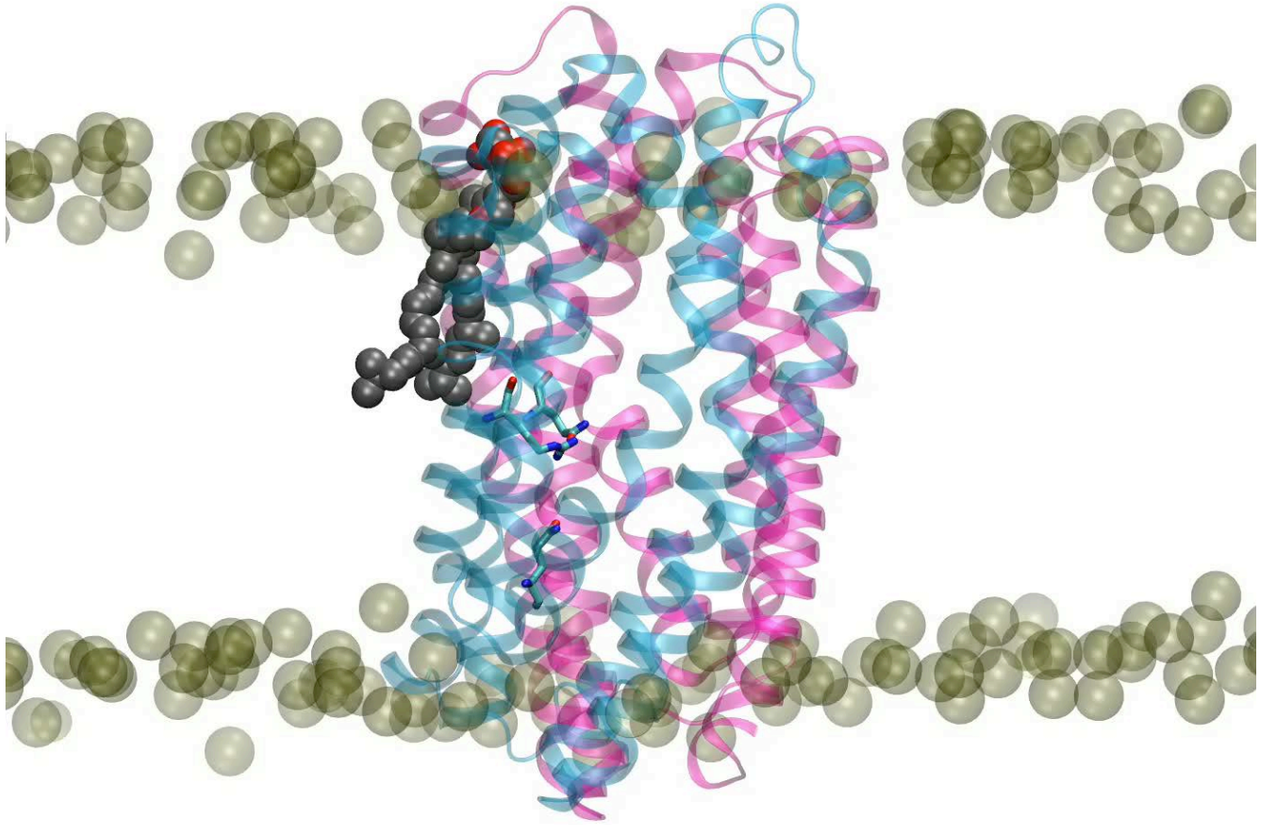
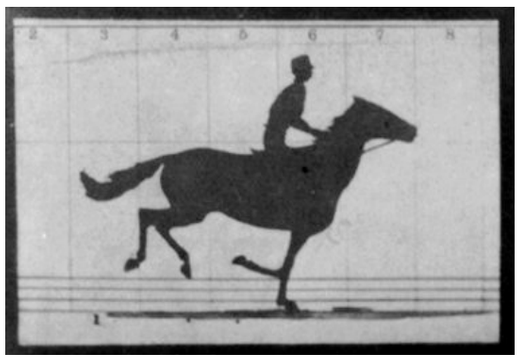


Structural information
Dynamic



Dynamics as time-resolved phenomenon



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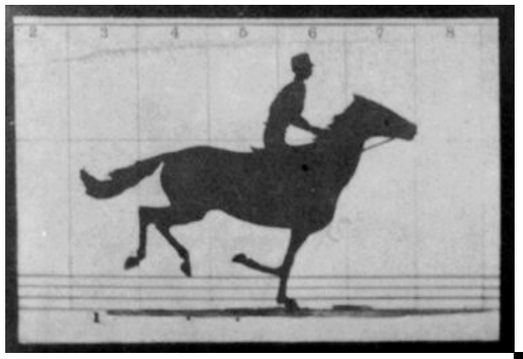
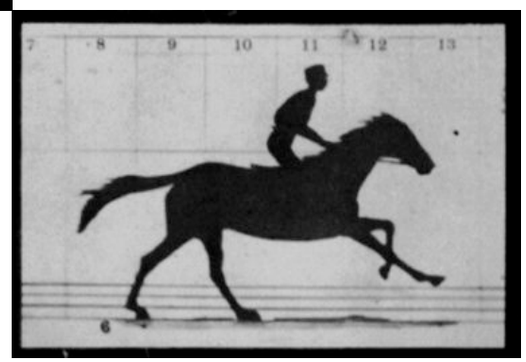
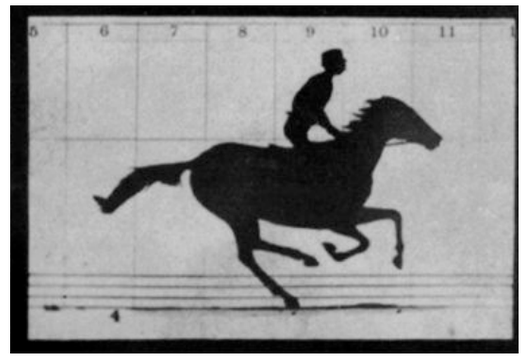
Dynamics as time-resolved phenomenon







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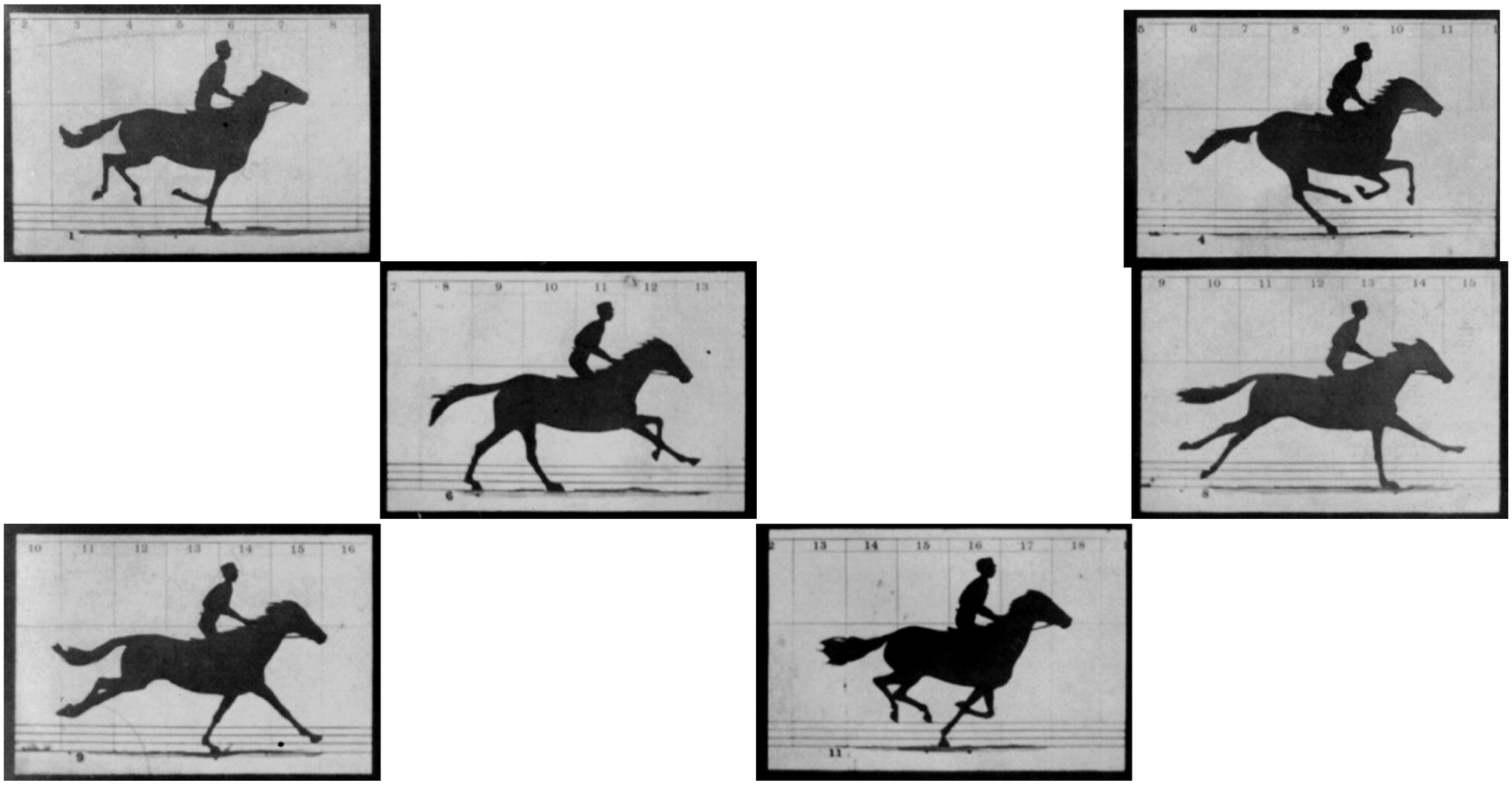

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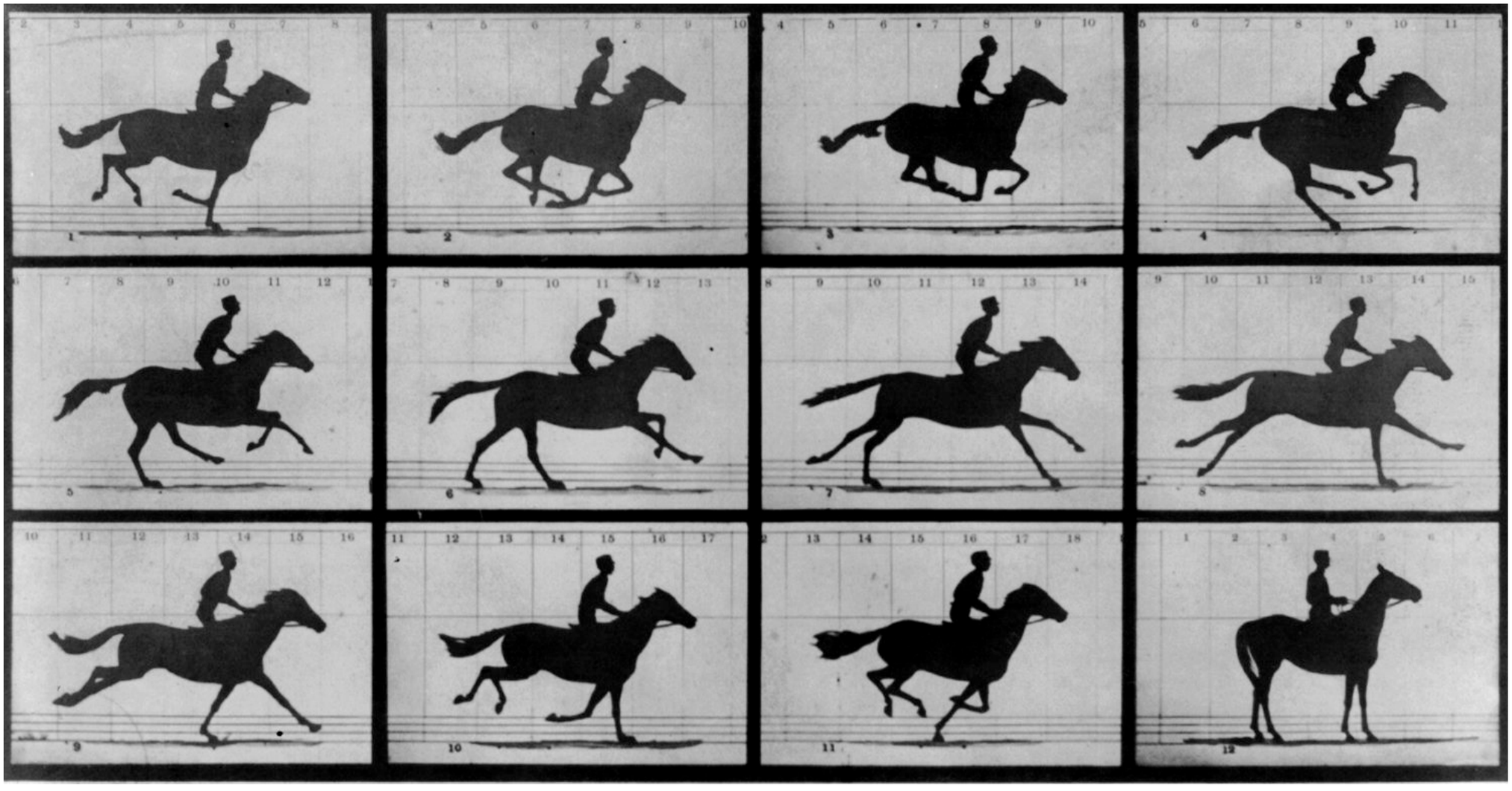

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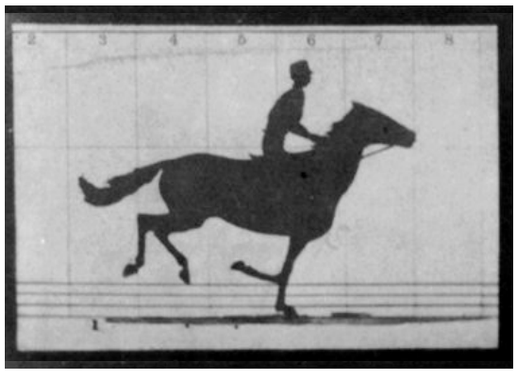

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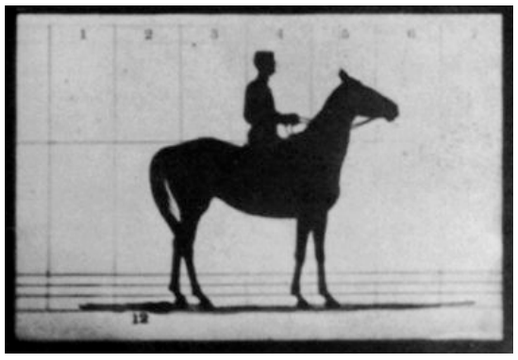

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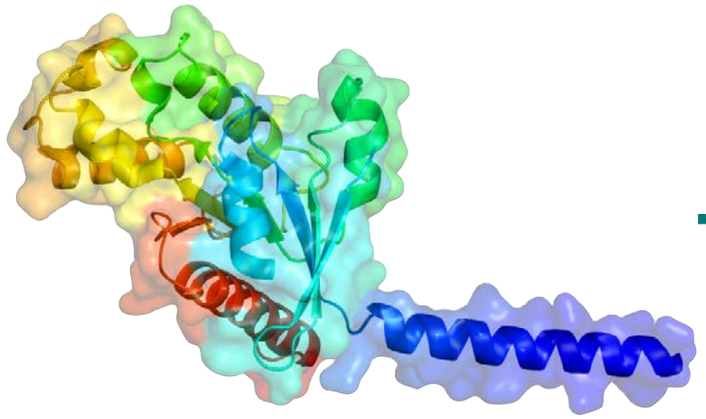
Principles of molecular dynamics simulations

How can we capture the dynamics of biomolecules?



Δt

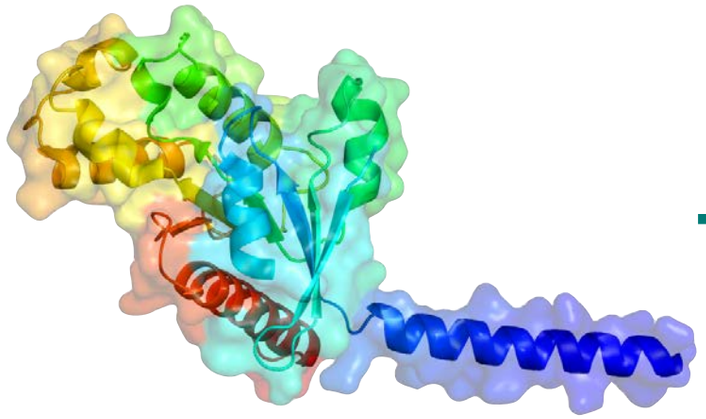
????

t_0

t_1

Newton to rescue

How can we capture the dynamics of biomolecules?



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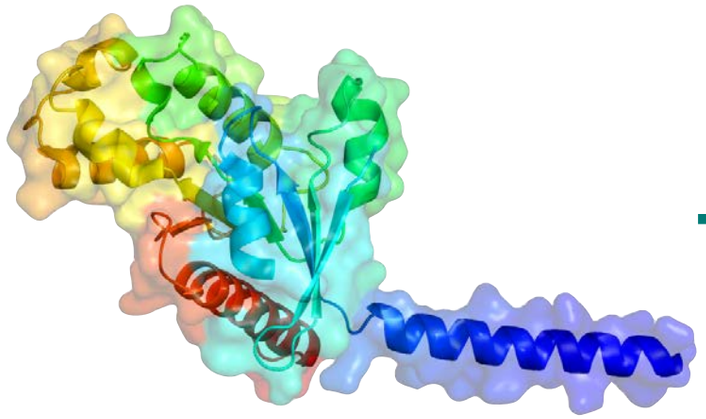


Δt

????

t_0

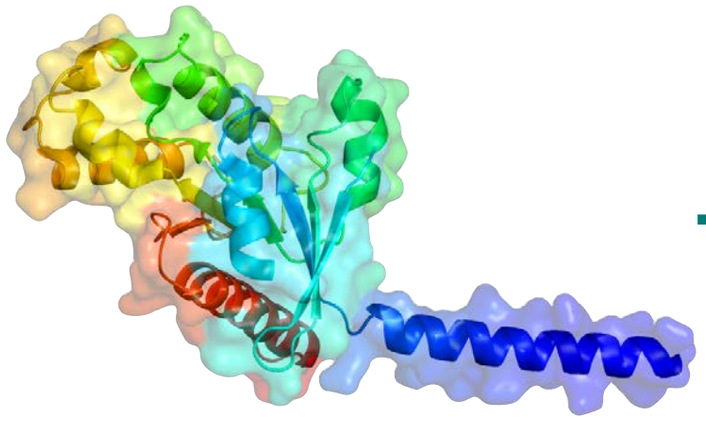
t_1

Mass
Coordinates
Velocities
Accelerations

Newton to rescue

Consider a protein at time t

Mass
Coordinates
Velocities
Accelerations



Δt

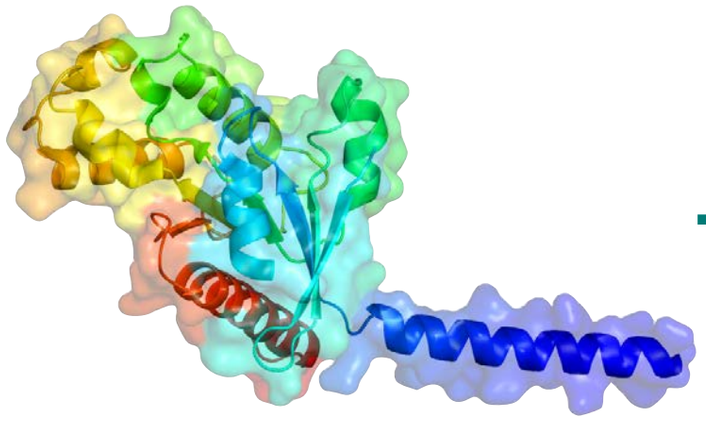
????

Where will all atoms of the protein be at time $t+\Delta t$?

Newton to rescue

Consider a protein at time t

Mass
Coordinates
Velocities
Accelerations



Δt

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$$F = ma$$

Newton to rescue

Consider a protein at time t

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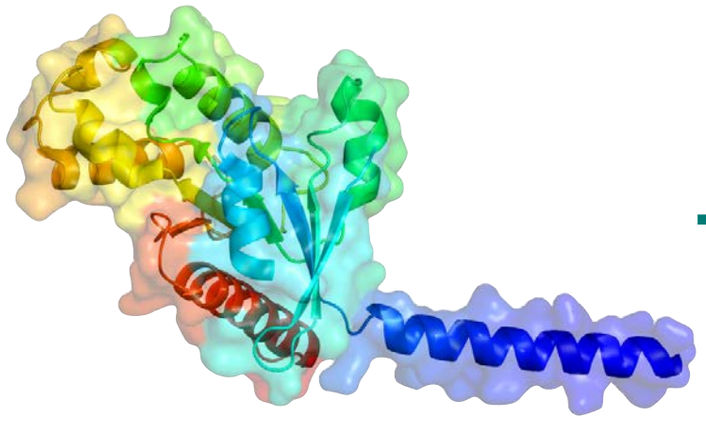


Δt

????

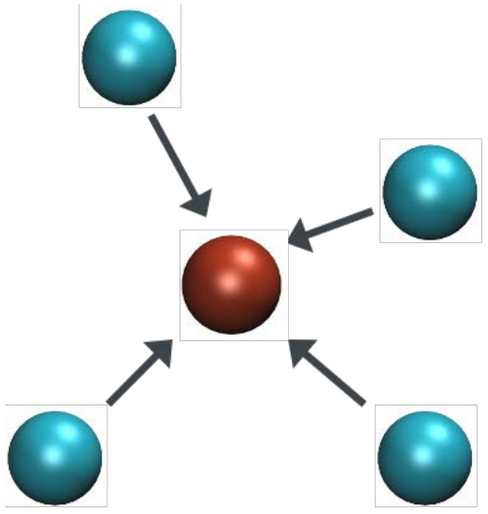
Where will all atoms of the protein be at time $t+\Delta t$?

$$F = ma$$

Solution: **discretised time step (Δt).**

$$r_i(t_0) \longrightarrow r_i(t_0+\Delta t) \longrightarrow r_i(t_0+2\Delta t) \longrightarrow r_i(t_0+3\Delta t) \longrightarrow r_i(t_0+n\Delta t)$$

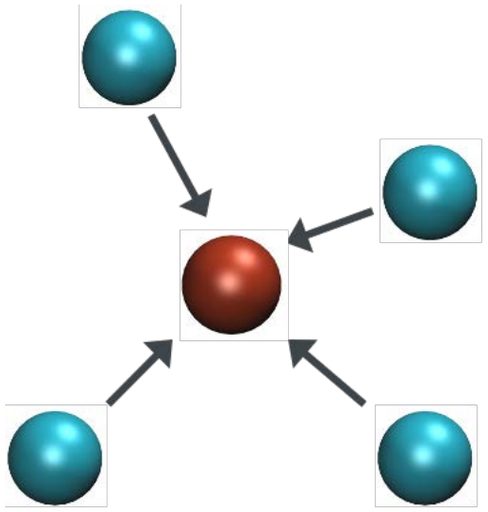
We need to calculate the force!



Potential energy

$$F = \frac{-\partial U(r)}{\partial r}$$

We need to calculate the force!



Potential energy

$$F = \frac{-\partial U(r)}{\partial r}$$

Potential energy or force field

$$U(r) = U_{Bond} + U_{Angle} + U_{Dihedral} + U_{Coulomb} + U_{VdW}$$

We need to calculate the force!

$$F = \frac{-\partial U(r)}{\partial r}$$

Our potential function or ‘force field’ is defined by **bonded** and non-bonded interactions.

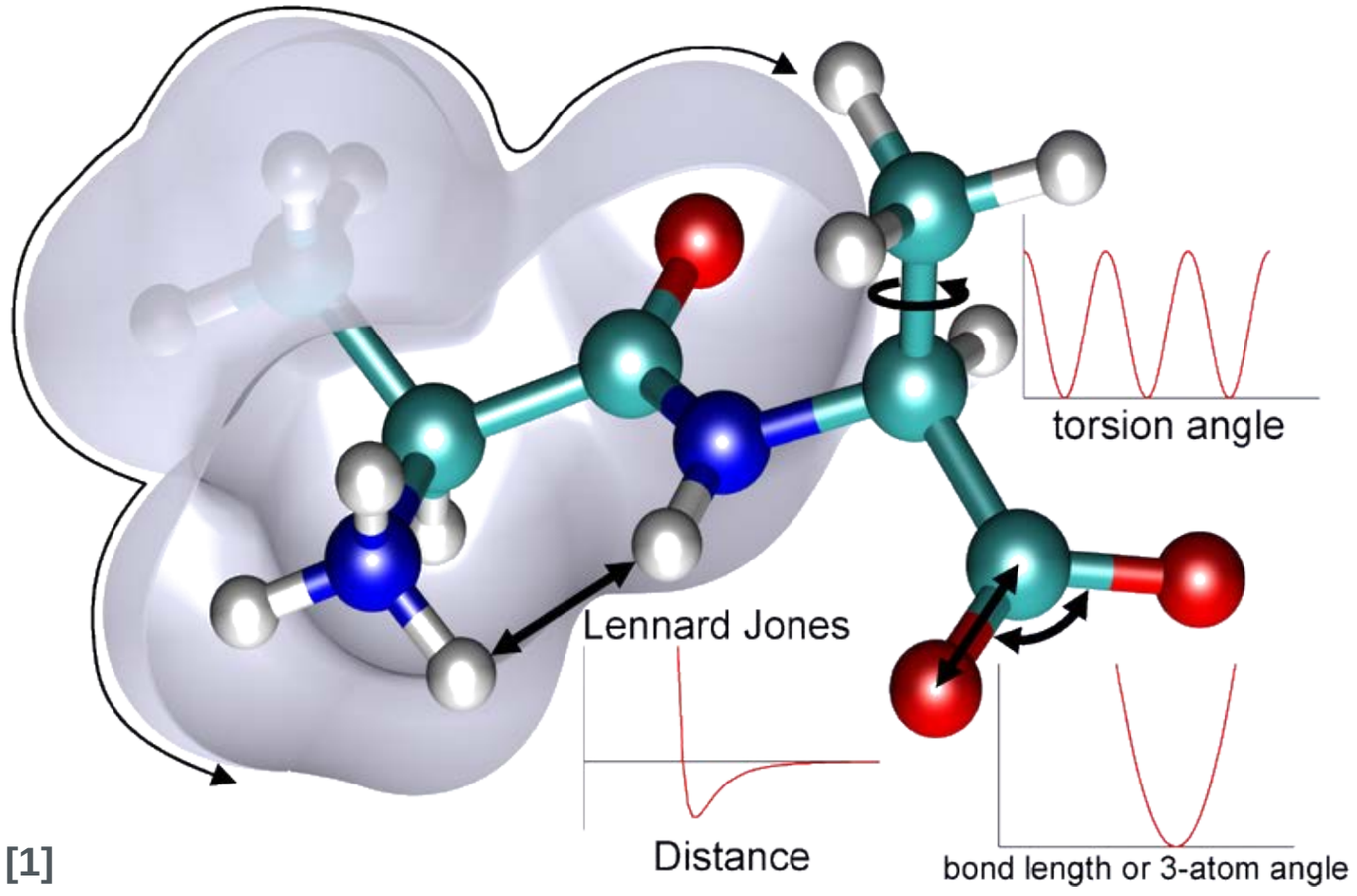
$$U(r) = U_{Bond} + U_{Angle} + U_{Dihedral} + U_{Coulomb} + U_{VdW}$$

We need to calculate the force!

$$F = \frac{-\partial U(r)}{\partial r}$$

Our potential function or ‘force field’ is defined by **bonded** and non-bonded interactions.

$$U(r) = \boxed{U_{Bond} + U_{Angle} + U_{Dihedral}} + U_{Coulomb} + U_{VdW}$$



[1]

[1] force field / Edboas CC BY-SA 3.0

We need to calculate the force!

$$F = \frac{-\partial U(r)}{\partial r}$$

Our potential function or ‘force field’ is defined by bonded and **non-bonded** interactions.

$$U(r) = U_{Bond} + U_{Angle} + U_{Dihedral} + U_{Coulomb} + U_{VdW}$$

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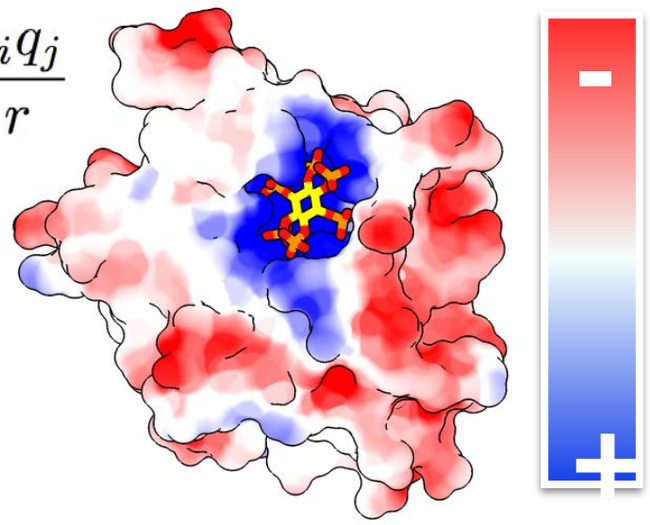
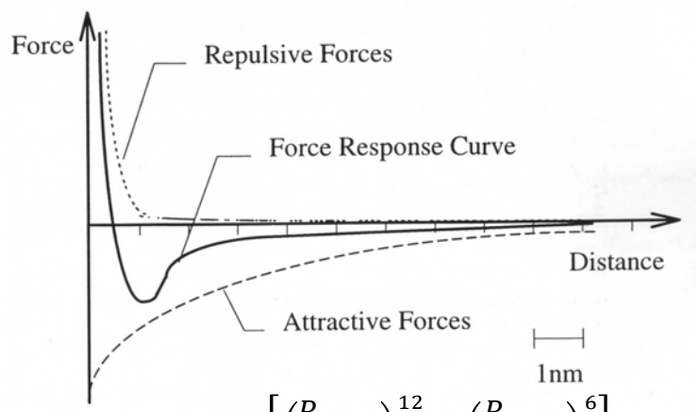
Electrostatic interaction

$$V_C = \frac{1}{4\pi\epsilon_0\epsilon_r}\frac{q_i q_j}{r}$$



van der Waals forces



$$U_{VdW} = \varepsilon\left[\left(\frac{R_{min_{ij}}}{r_{ij}}\right)^{12} - \left(\frac{R_{min_{ij}}}{r_{ij}}\right)^{6}\right]$$

We need to calculate the force!

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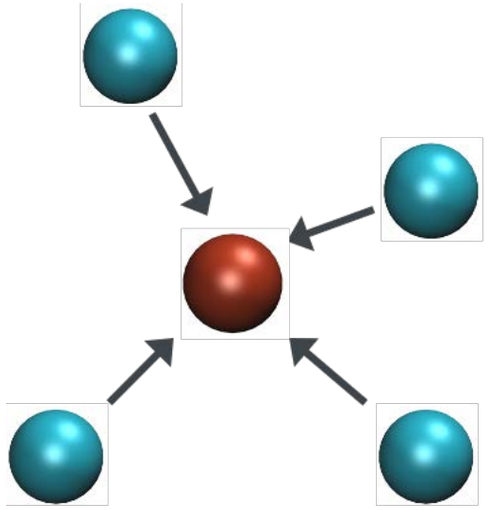
$$U = \sum_{Bond} k_b(b - b_0)^2 + \sum_{Angle} k_\theta(\theta - \theta_0)^2 + \sum_{Dihedral} k_\varphi[1 + \cos(n\varphi - \delta)]$$
$$+ \sum_{Coulomb} \frac{q_i q_j}{\varepsilon r_{ij}} + \sum_{VdW} \varepsilon \left[\left(\frac{R_{min_{ij}}}{r_{ij}}\right)^{12} - \left(\frac{R_{min_{ij}}}{r_{ij}}\right)^{6}\right]$$

Basic molecular dynamics simulation algorithm



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Basic molecular dynamics simulation algorithm

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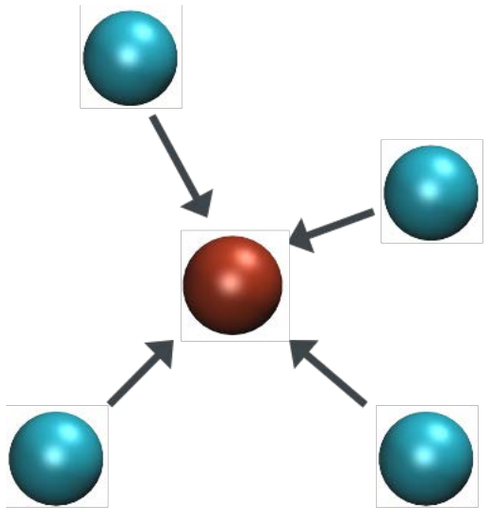

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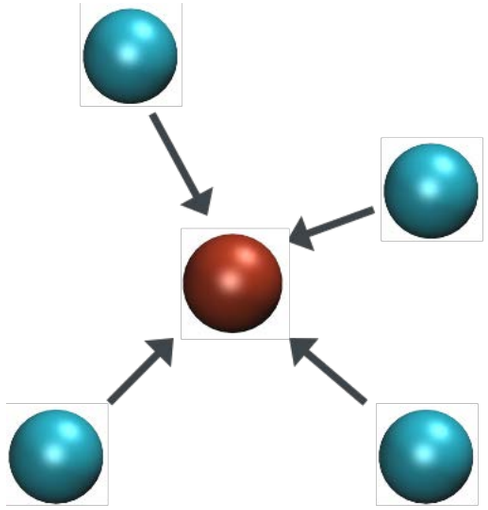

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Basic molecular dynamics simulation algorithm

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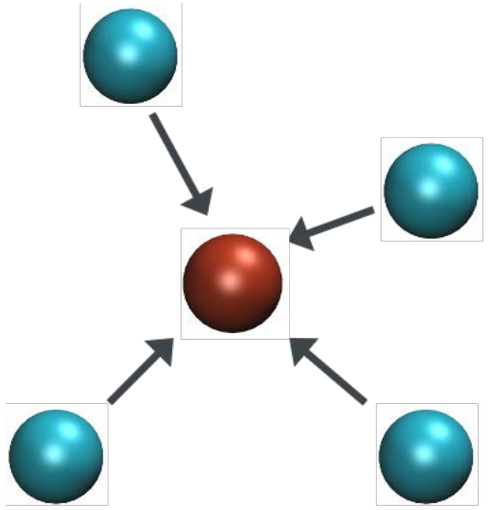
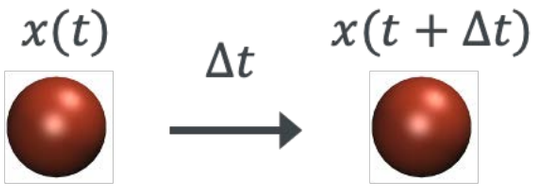


$$F = \frac{-\partial U(r)}{\partial r}$$

$$a = \frac{F}{m}$$

Basic molecular dynamics simulation algorithm



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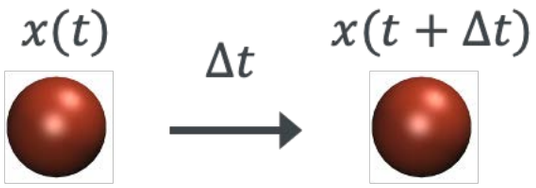
Basic molecular dynamics simulation algorithm



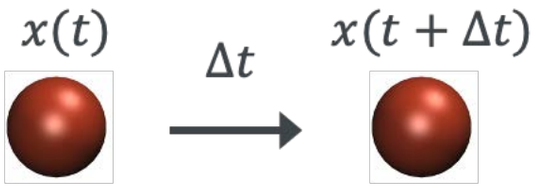
Simple algorithm to propagate system:

1) Particle has position **x** and velocity **v** at time t

2) Determine forces and acceleration acting on the particle

3) Move the particle for time step Δt

Basic molecular dynamics simulation algorithm



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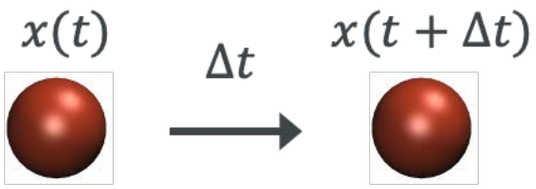
$$x(t+\Delta t) = x(t) + v(t)\Delta t + \frac{1}{2}a(t)\Delta t^2$$

Basic molecular dynamics simulation algorithm



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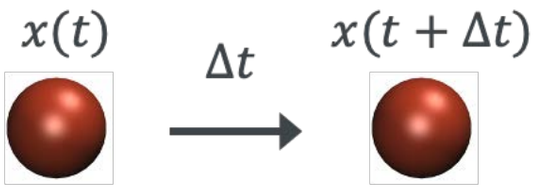
Basic molecular dynamics simulation algorithm



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$$v(x+\Delta t) = \frac{x(t+\Delta t) - x(t)}{\Delta t}$$

How small/large can ∆t be?

Molecular dynamics simulations: Algorithm

Initial coordinates **r** and velocities **v**

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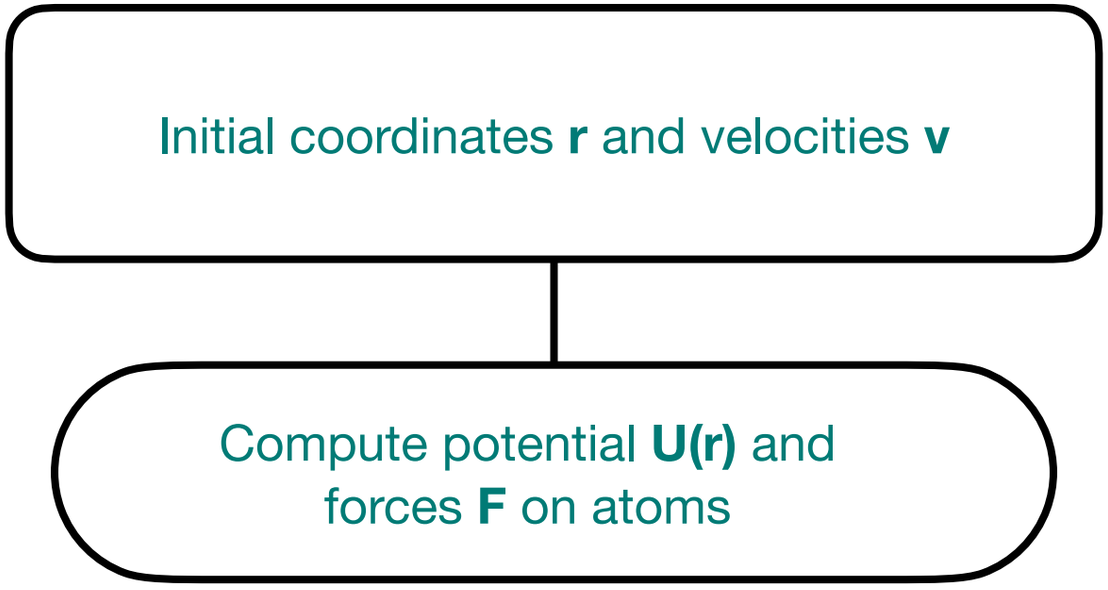
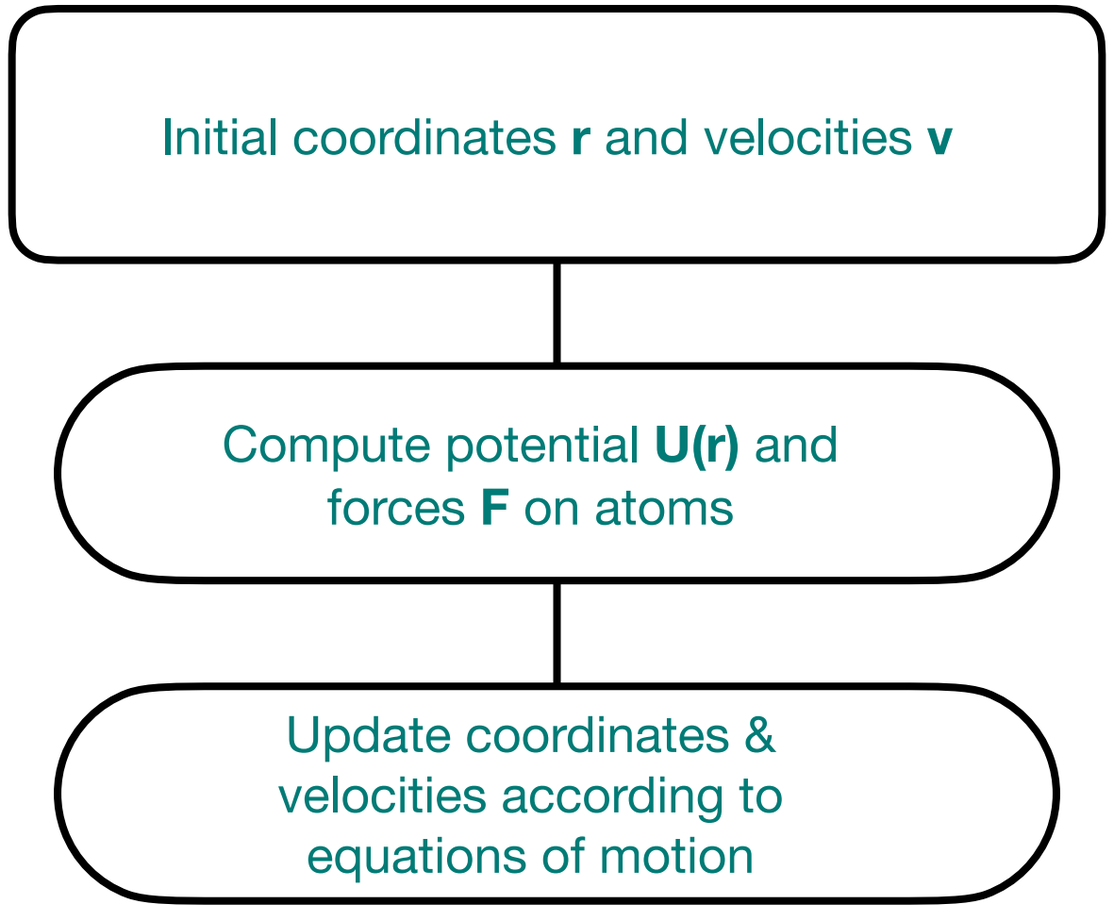
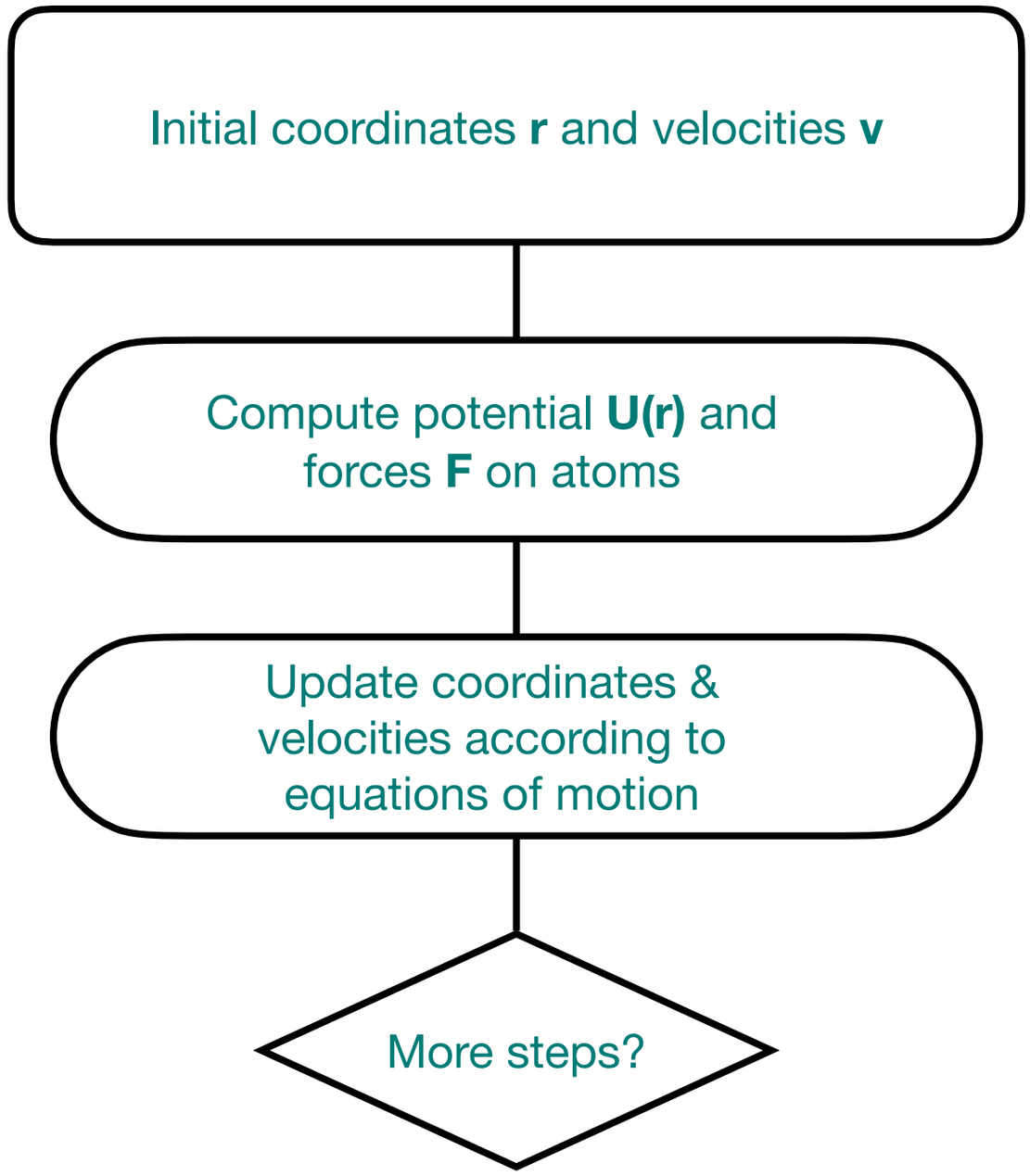
Molecular dynamics simulations: Algorithm



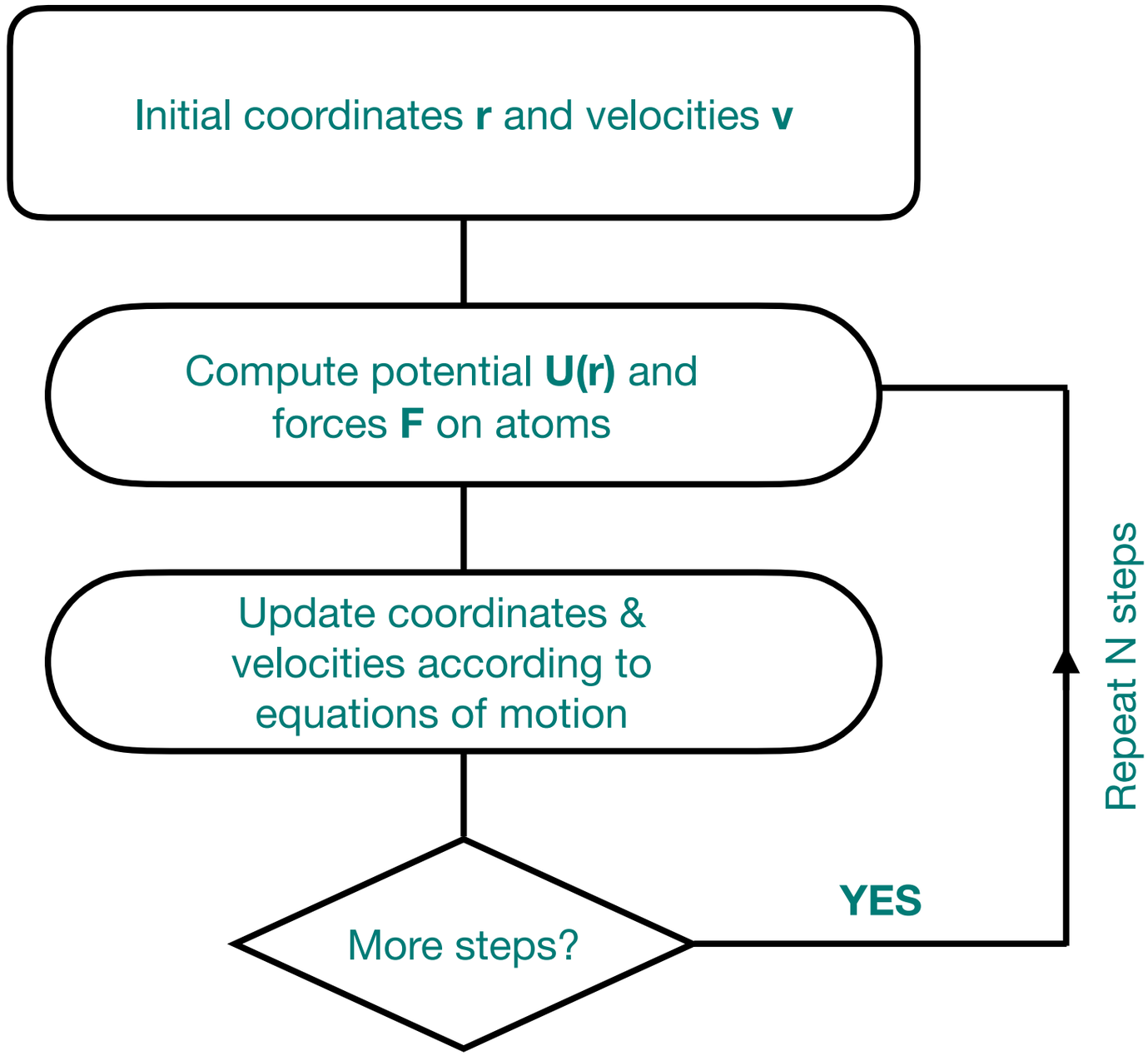
Molecular dynamics simulations: Algorithm



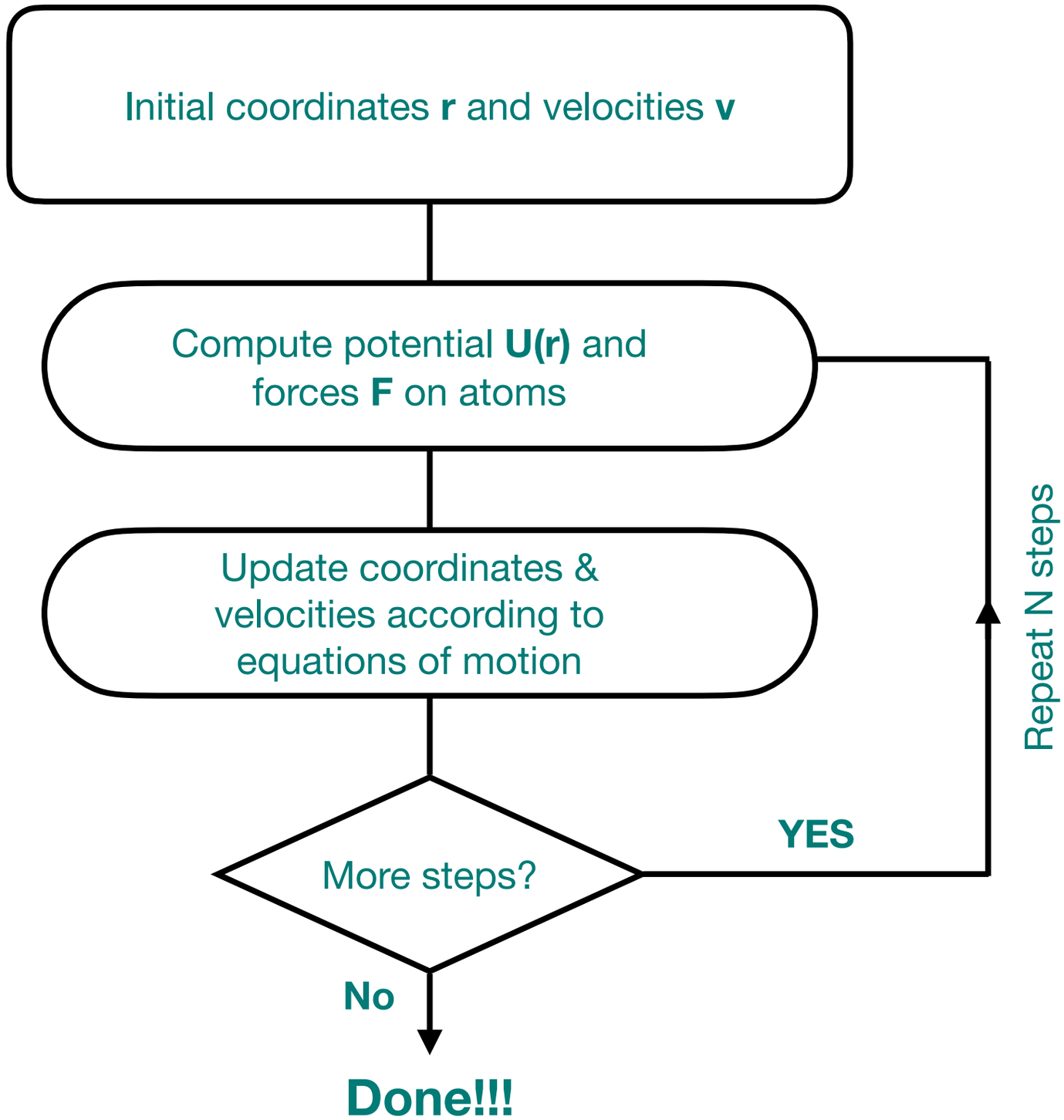
Molecular dynamics simulations: Algorithm



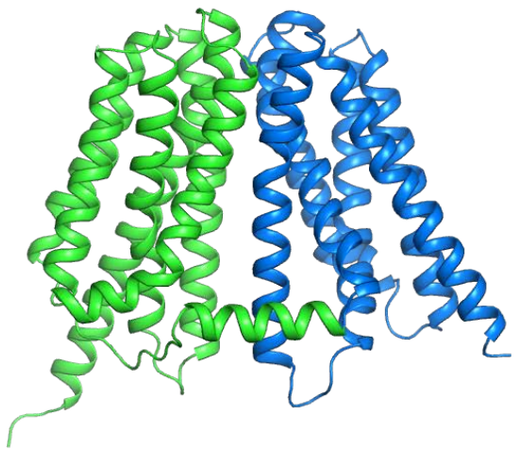
Molecular dynamics simulations: Algorithm



Molecular dynamics simulations: Algorithm



How to run an MD simulation?



Protein preparation

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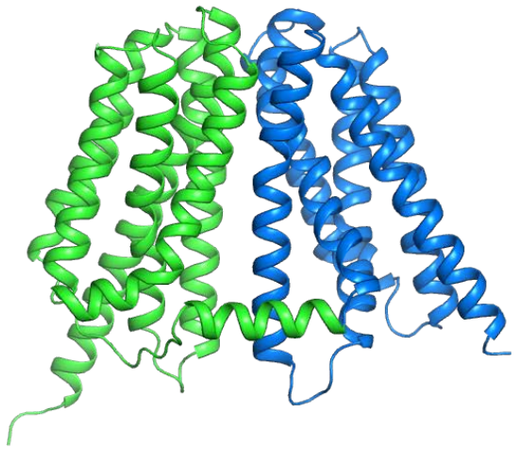
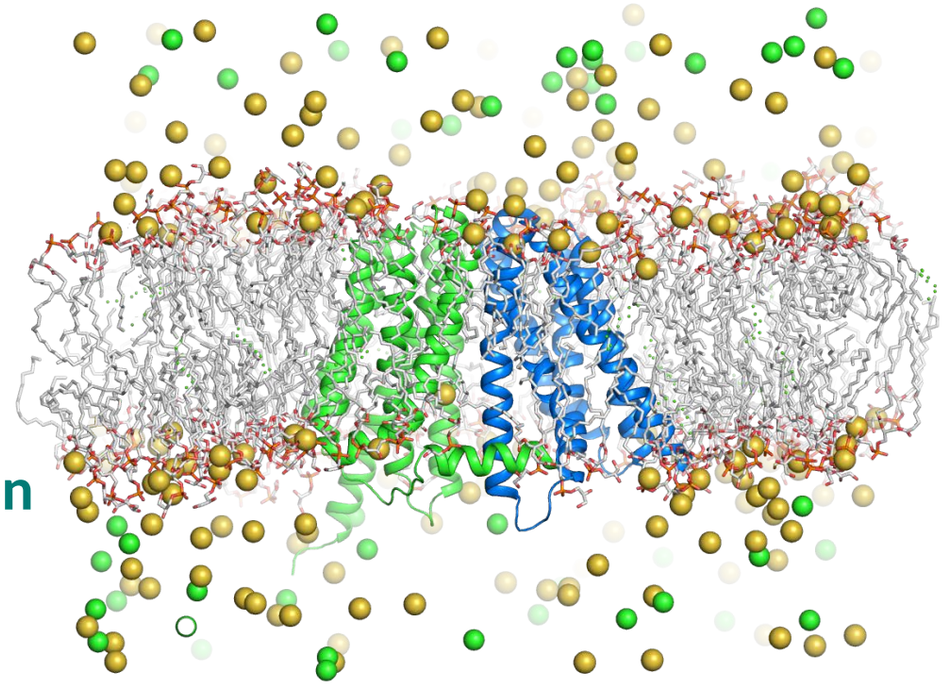
How to run an MD simulation?



Protein preparation

Add membrane

And ions
to reach physiological concentration



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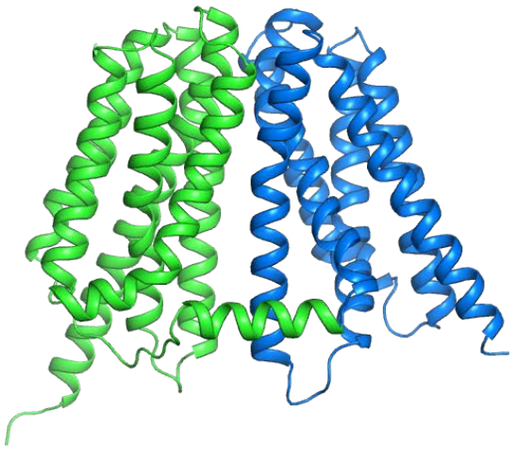
How to run an MD simulation?



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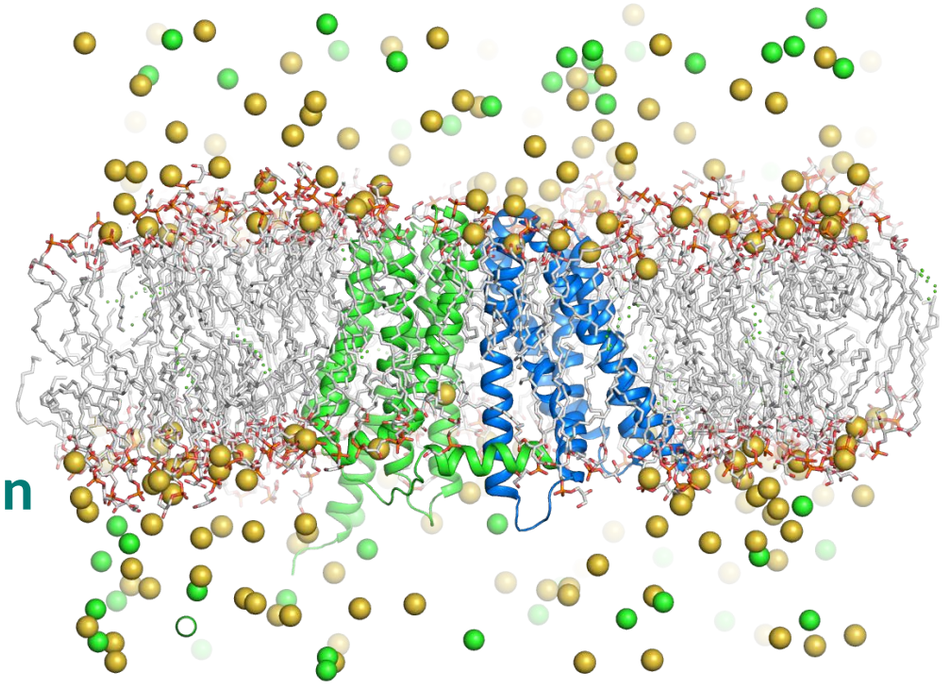
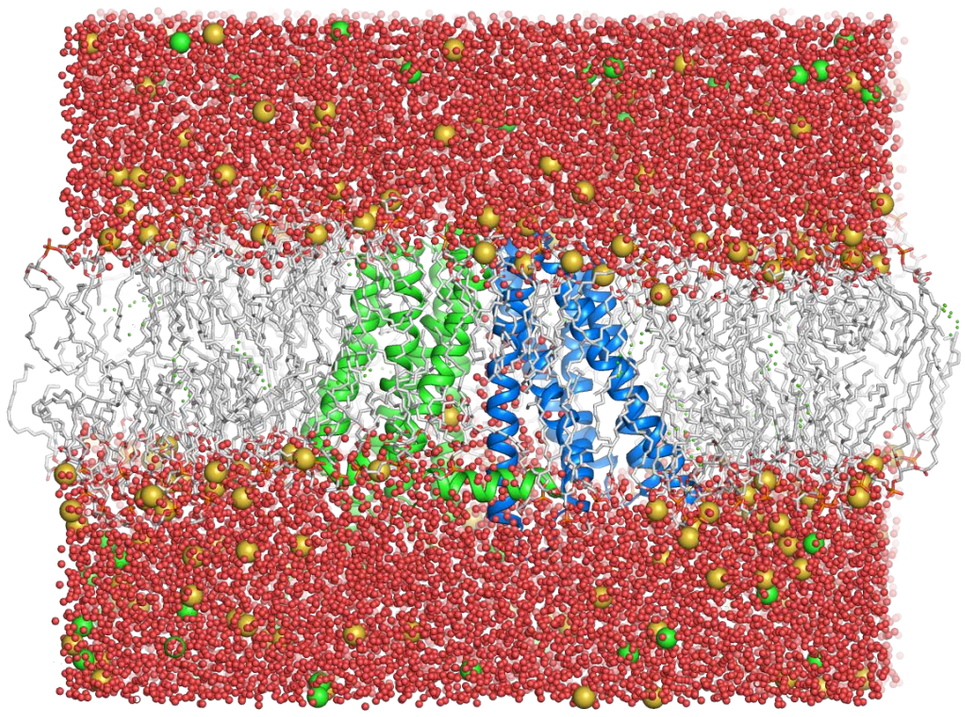


Add water



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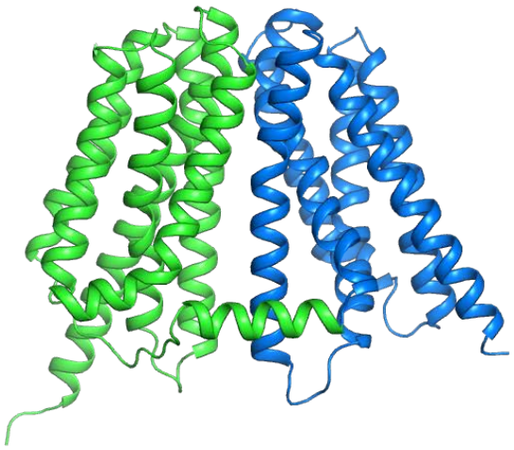

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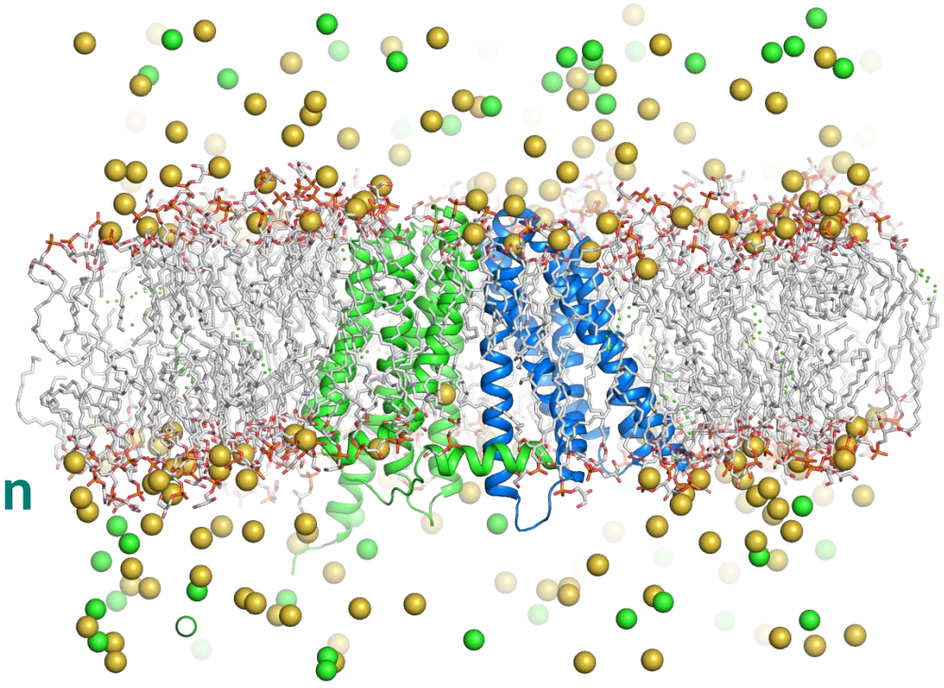
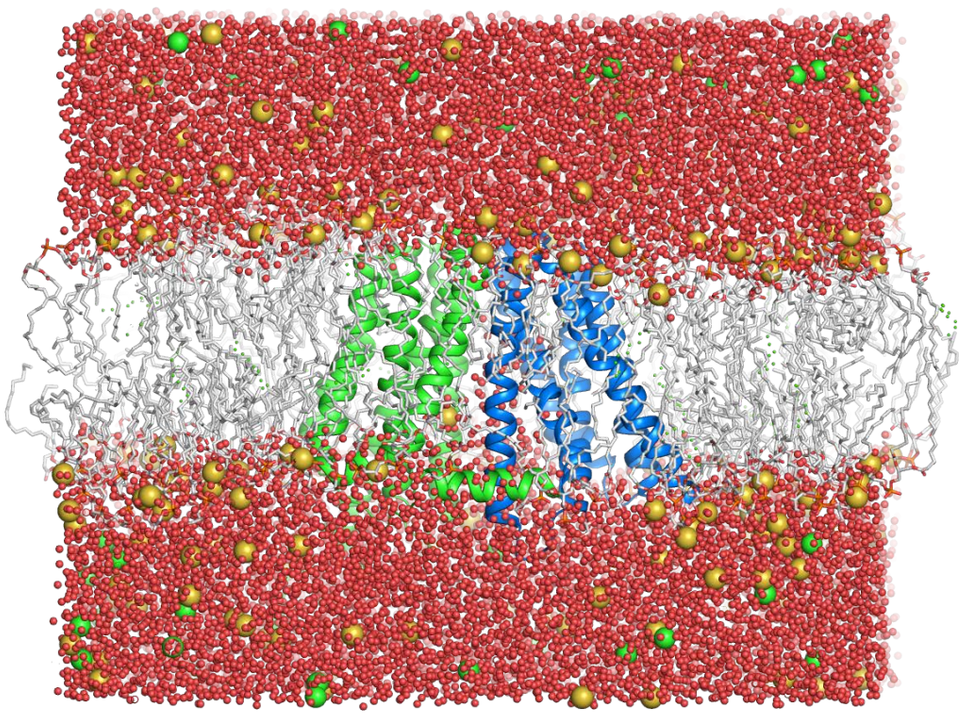
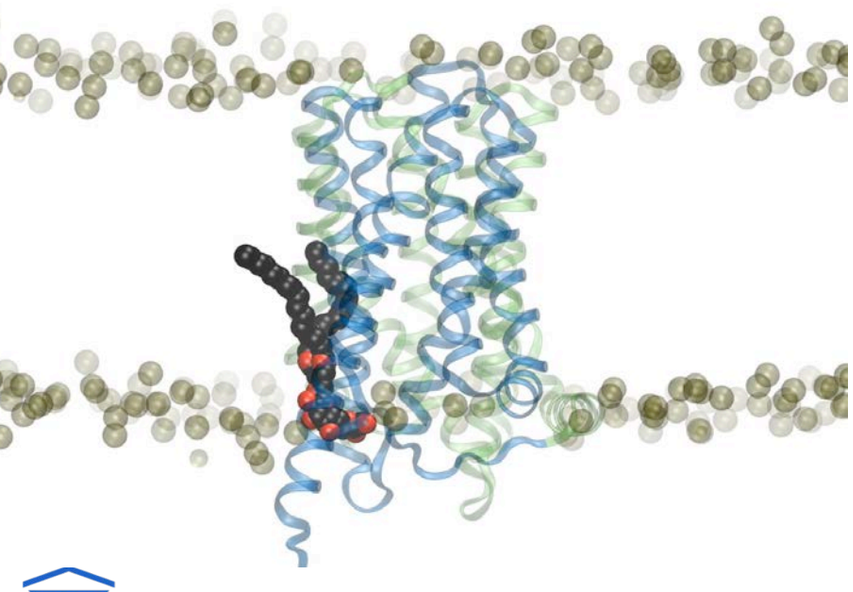


Add water



Run the simulation



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Membrane protein structure as starting point

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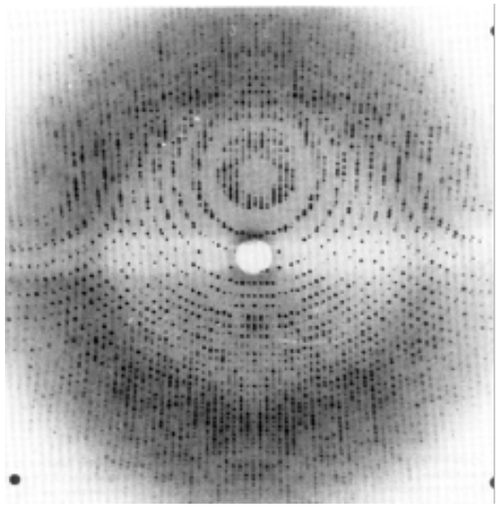
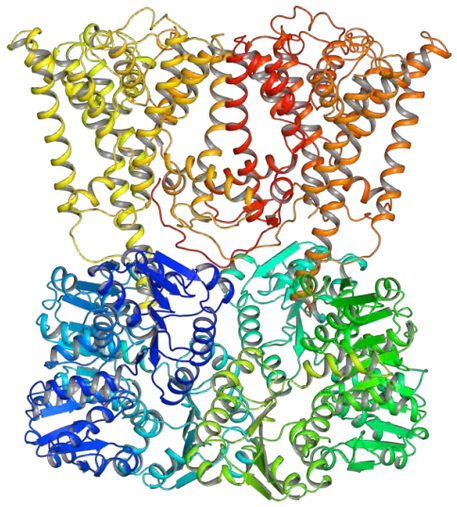
Membrane protein structure as starting point

X-ray crystallography





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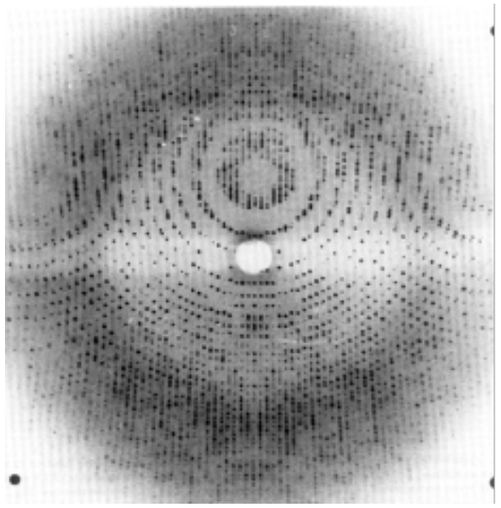
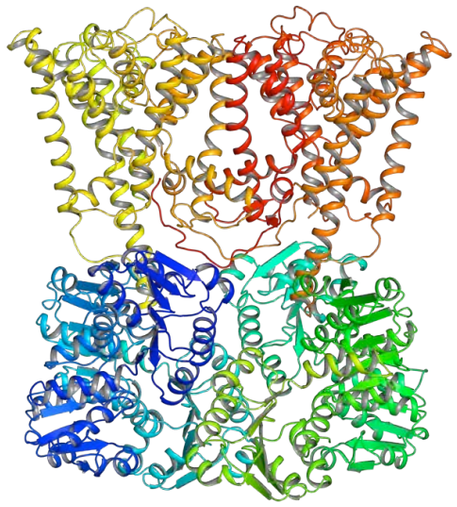
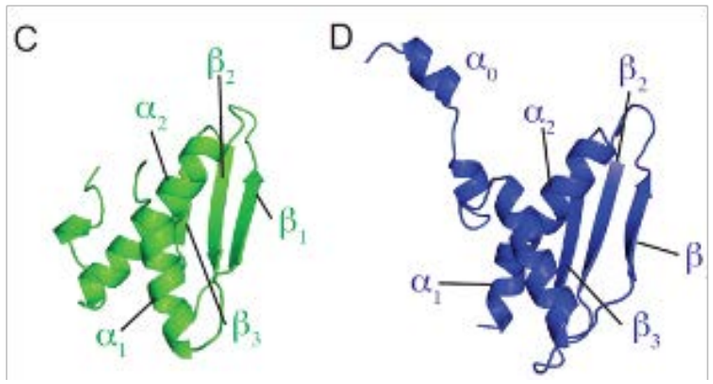




NMR



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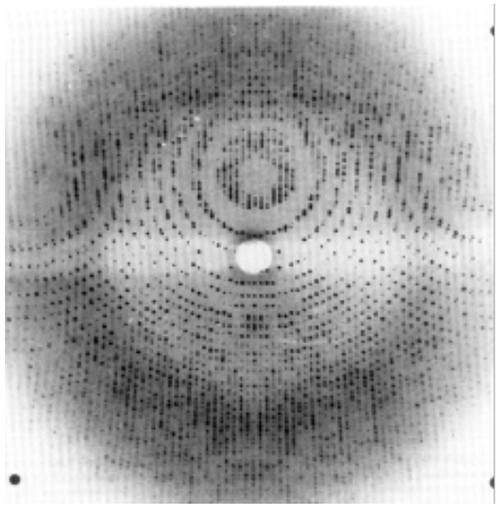

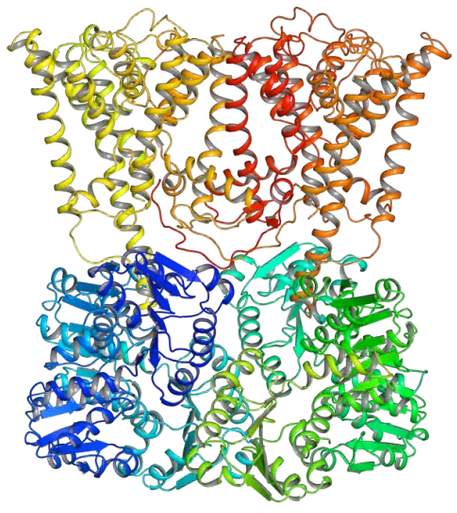

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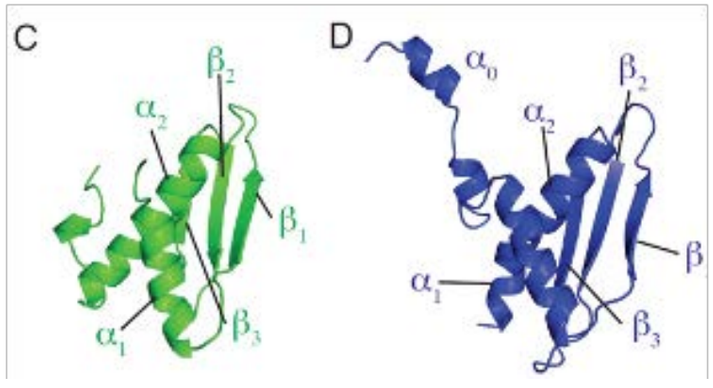
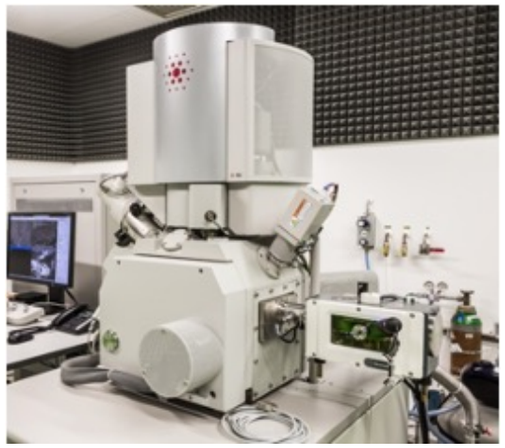
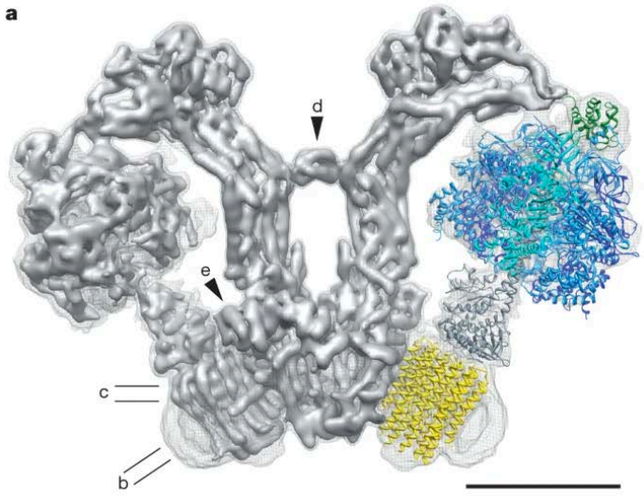


Cryo-EM





Membrane protein structure as starting point

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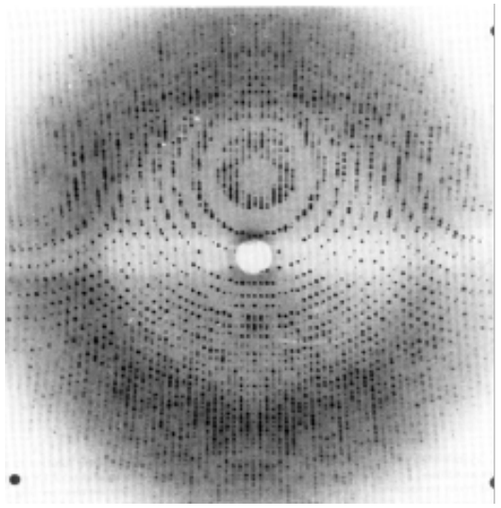

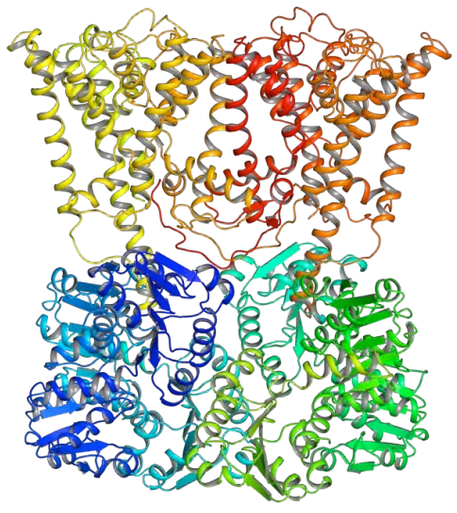

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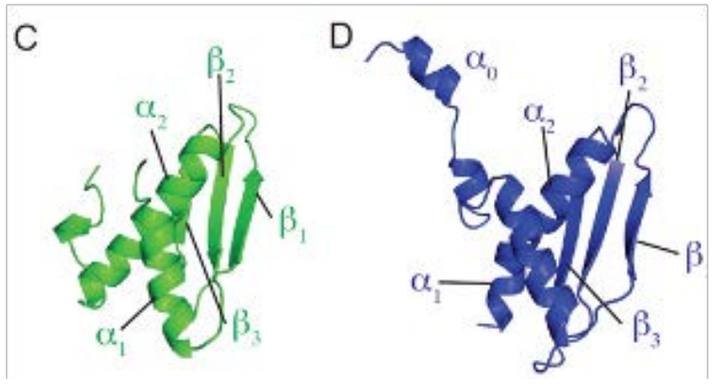

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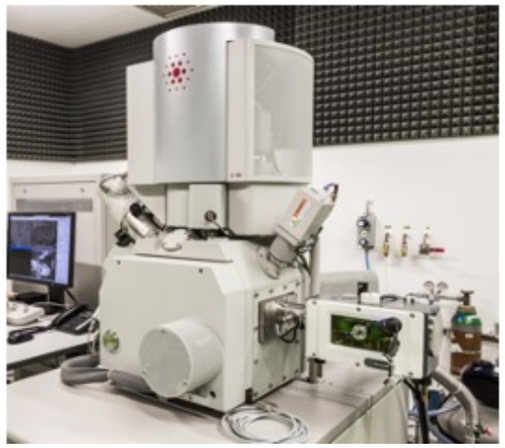
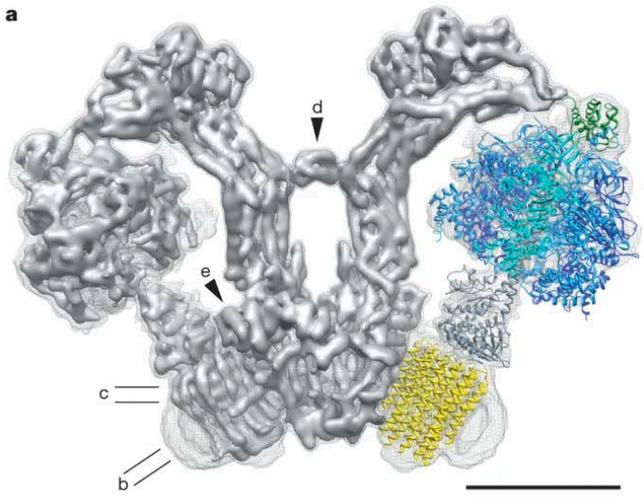
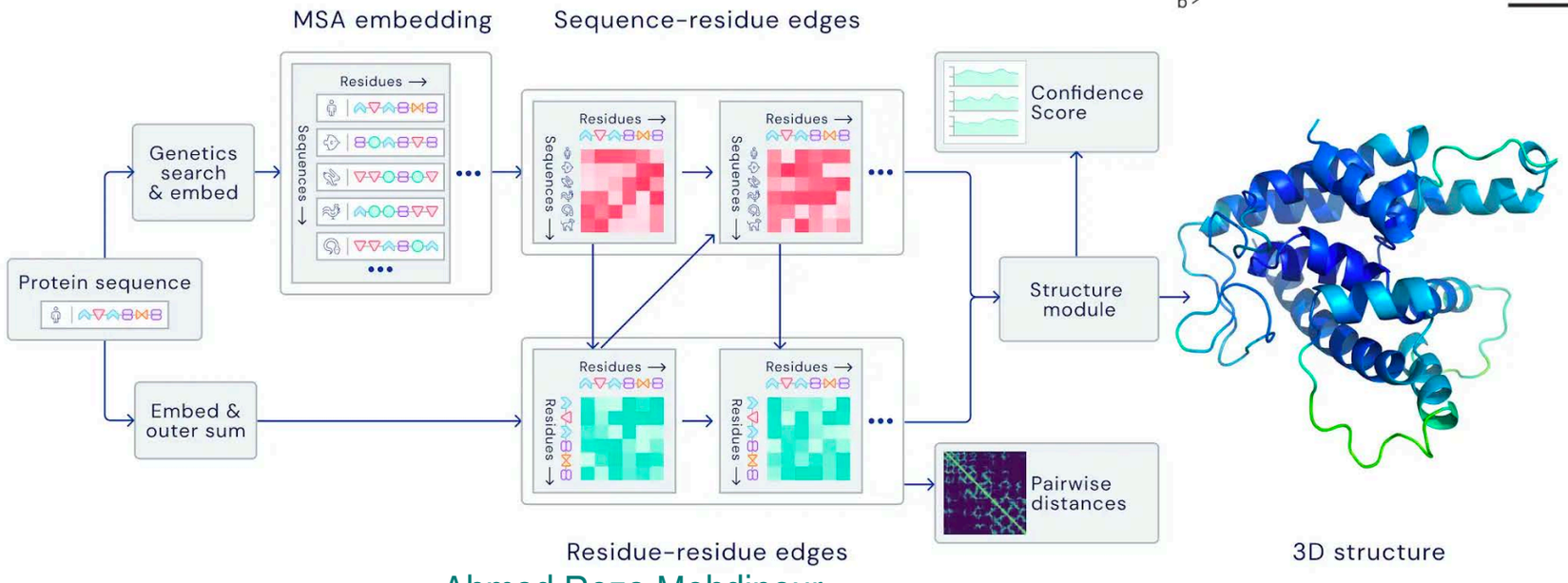




ML/AI-based structure prediction



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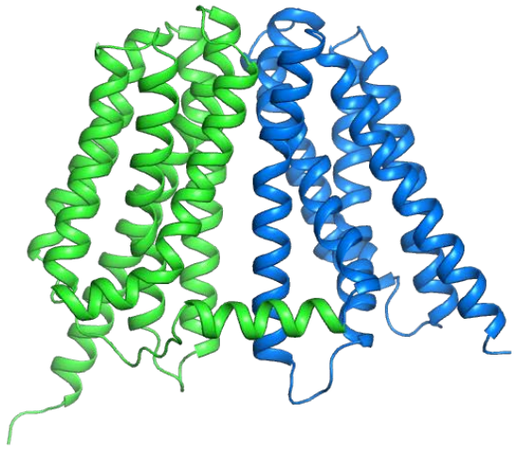
Protein preparation

Protein preparation



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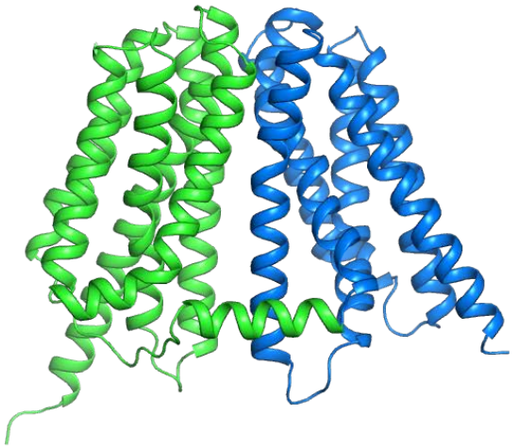
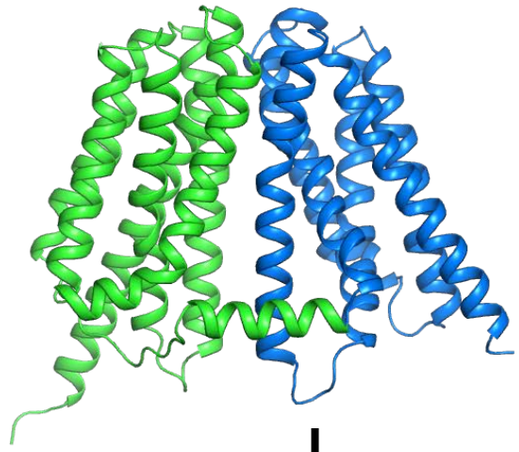


Structure refinement:

1. Add missing side-chains
2. Add missing loop

Protein preparation

Protein preparation



Structure refinement:

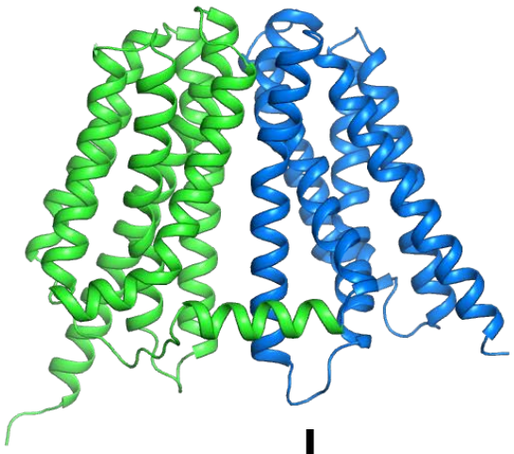
1. Add missing side-chains
2. Add missing loop

Add hydrogen atoms

1. Titrable residues?
2. pKa calculations

Protein preparation

Protein preparation



Structure refinement:

1. Add missing side-chains
2. Add missing loop

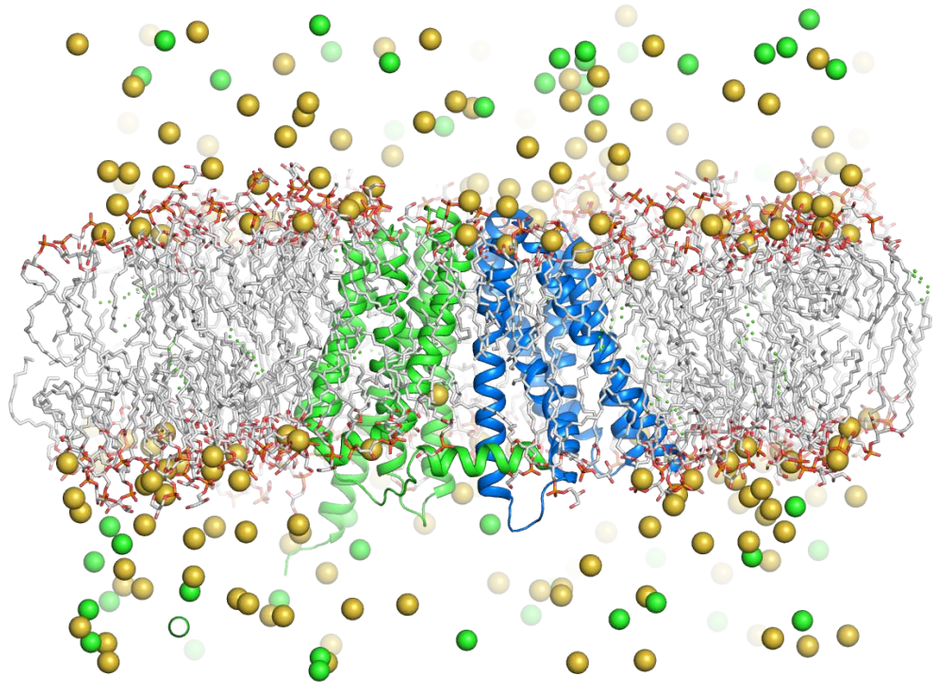
Add hydrogen atoms

1. Titrable residues?
2. pKa calculations

Structure minimisation:

1. Removing steric clashes

Add membrane



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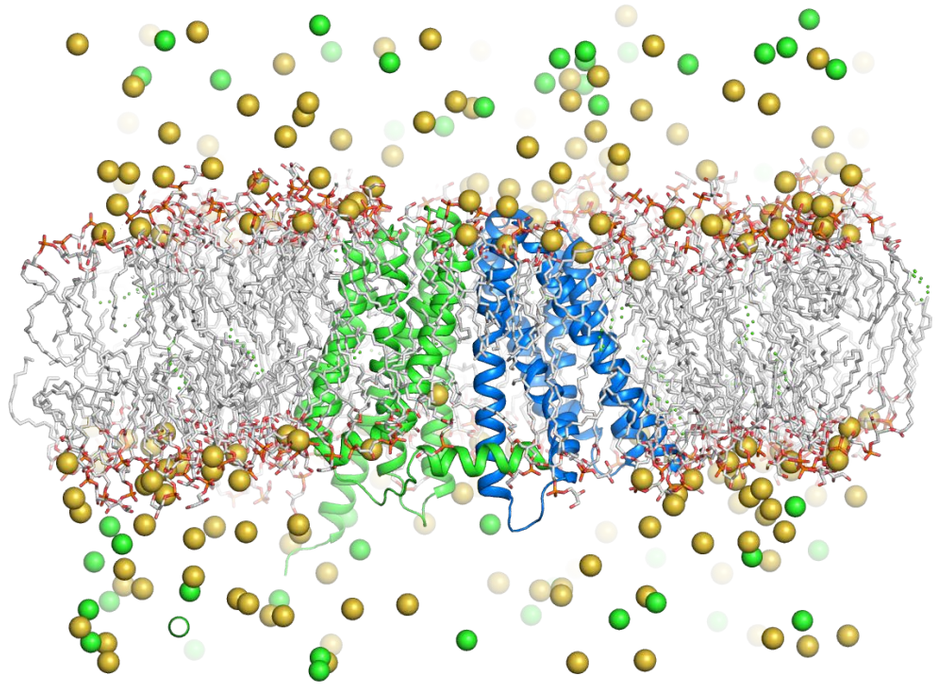
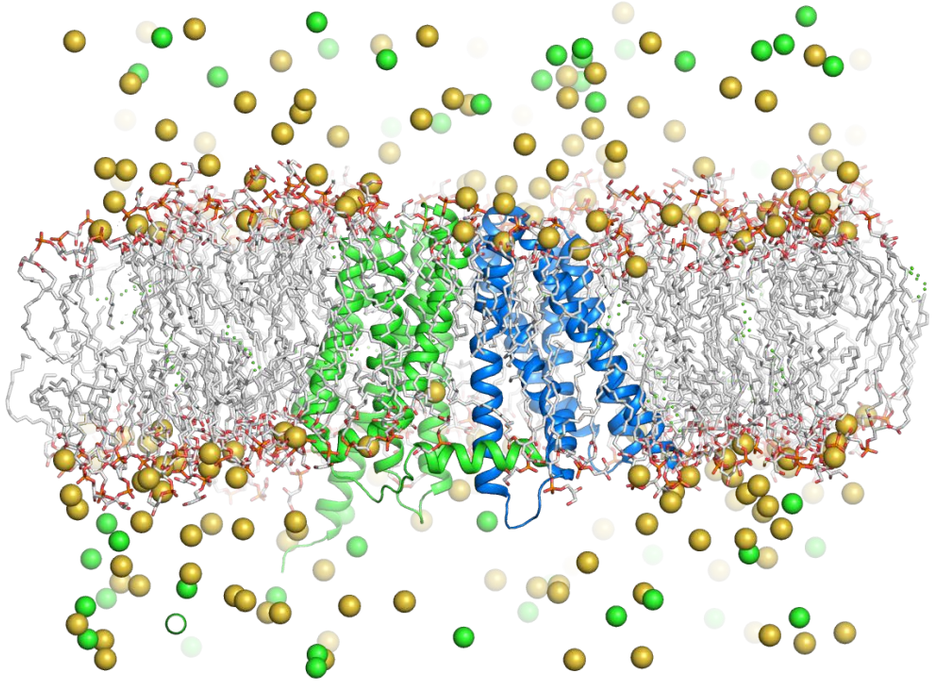
Add membrane



Complexity of membrane composition

1. Homogenous membrane
2. Heterogeneous membrane

Add membrane



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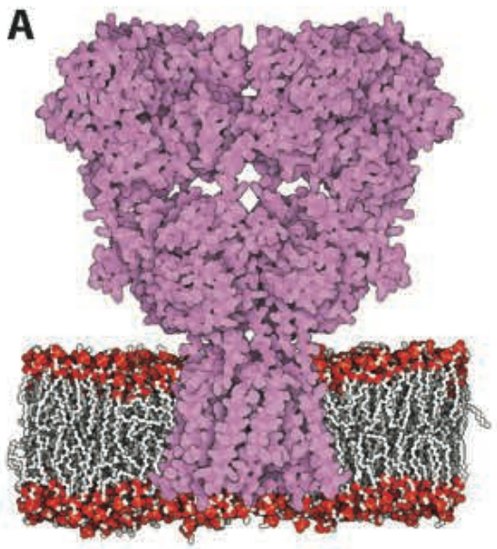
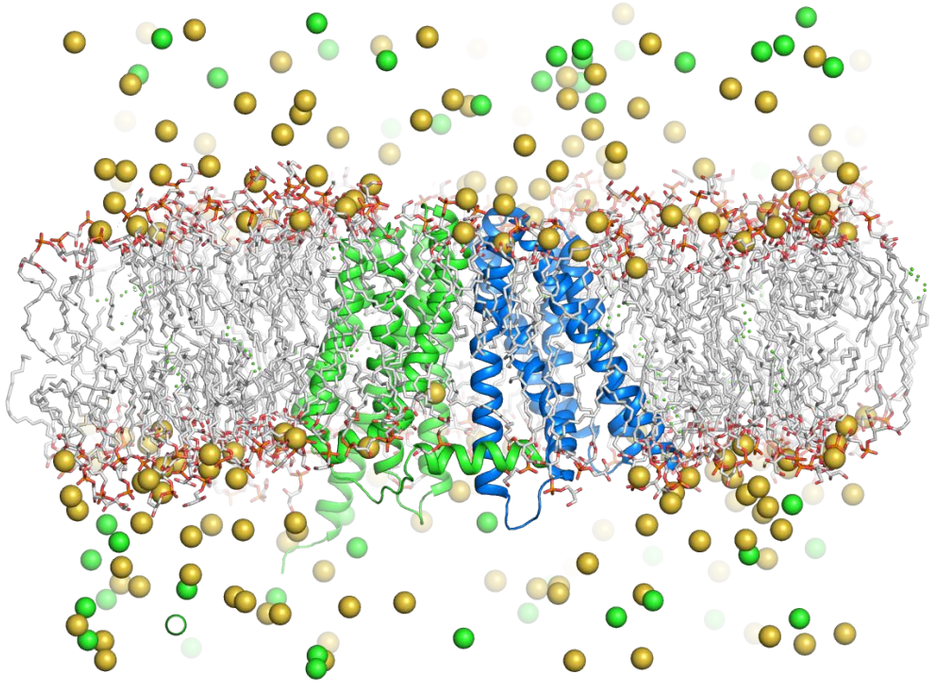


Add membrane



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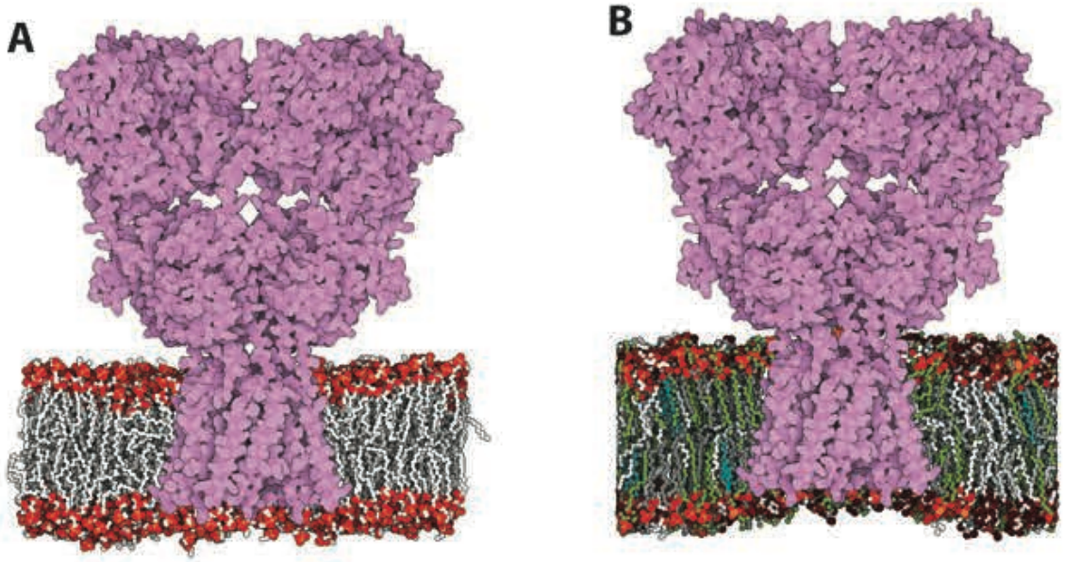

Add water: full system

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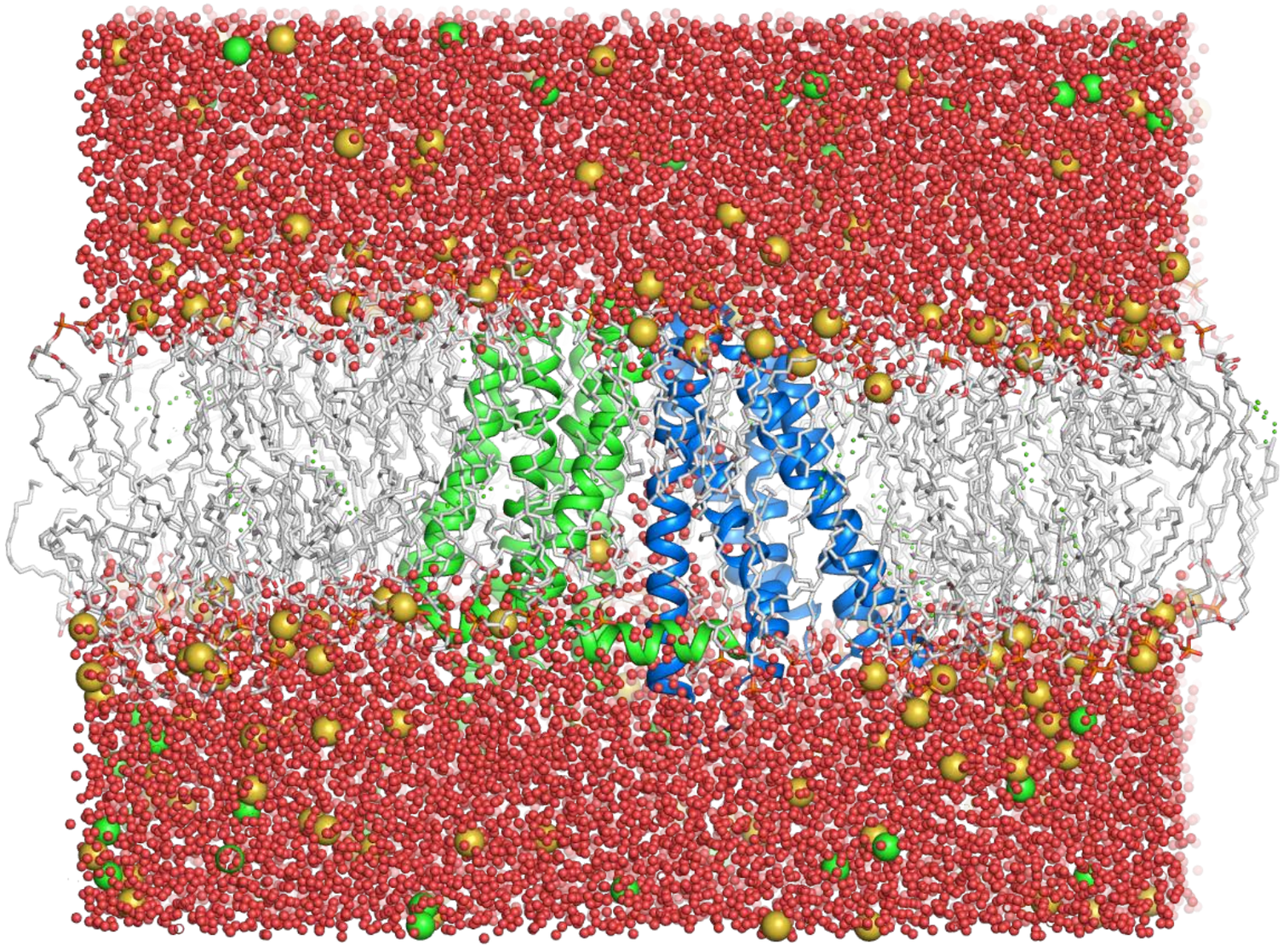
Add water: full system



Engines to run MD

openmm/**openmm**

OpenMM is a toolkit for molecular simulation using high performance GPU code.

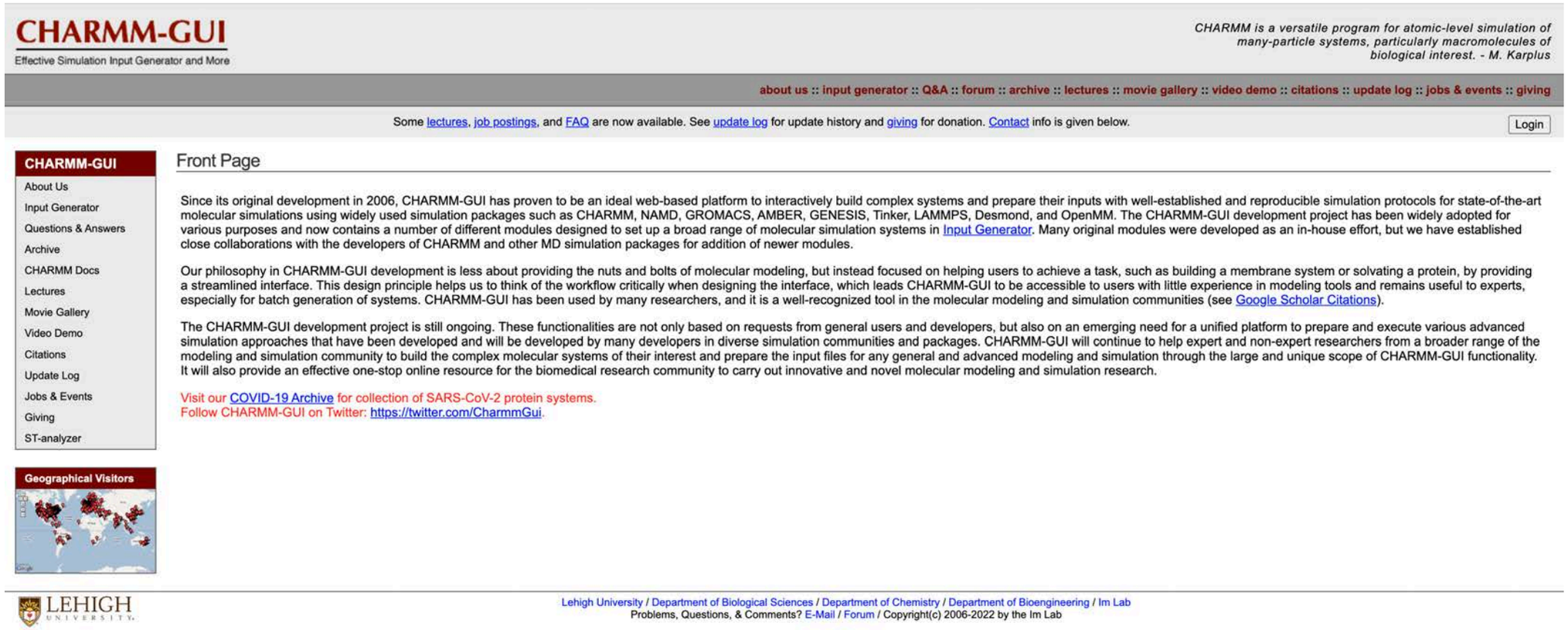
NAMD
Scalable Molecular Dynamics

GROMACS
fast, flexible & free

AMBER MD

Molecular Dynamics Simulations
HARMM

A web-server to setup your system



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A web-server to setup your system

Membrane Builder

Bookmark this link, if you want to comeback to this page

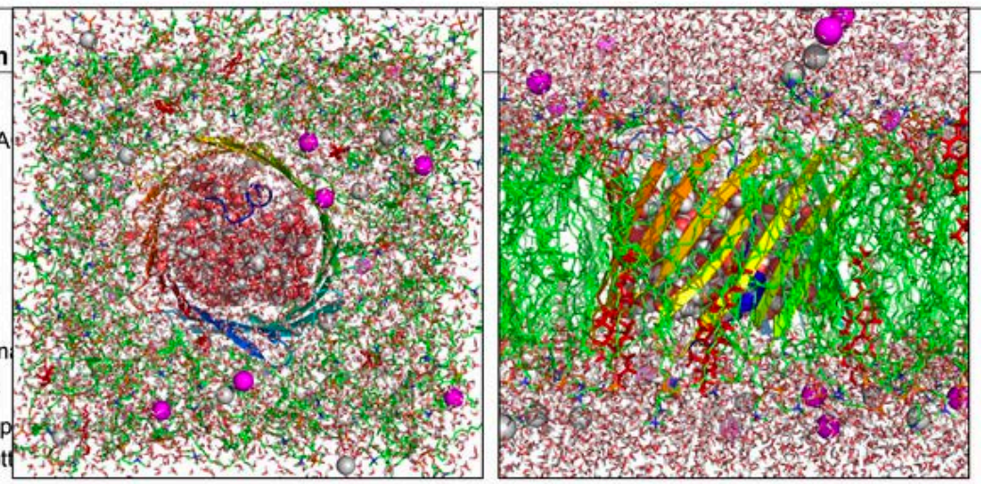
PDB Info | STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 | STEP 6

download .tgz

Lipid PDB: step4_lipid.pdb (view structure)
Assembly Input: step5_assembly.inp
Assembly Output: step5_assembly.out
System Information: step5_assembly.str
Assembled PSF: step5_assembly.psf
XPLOR PSF: step5_assembly.xplor.psf
Assembled CRD: step5_assembly.crd
Assembled PDB: step5_assembly.pdb (view structure)

Determined System

# of Atoms	
Crystal Type	TETRA
System Size	A
	B
	C
Crystal Angle	Alpha
	Beta
	Gamm
Lipid	POPC
# of Lipids	on Top
	on Bott
# of Water	7205
# of POT Ion	19
# of CLA Ion	21
Z Center	-1.8245



Assembled structure of protein/membrane complex. Spheres represents potassium (magenta) and chloride (gray) ions. Pore water molecules are represented as spheres as well (red and white). Cholesterols are colored in red.

Center of the system along the Z axis

Equilibriation Options:

- (•) Generate grid information for PME FFT automatically
- ( ) Explicit grid information for PME FFT

X Y Z

- (•) NPAT ensemble
- ( ) NPgT ensemble

Sufrace Tension 10 (dyne/cm)

Temperature: 303.15 K

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A web-server to setup your system

Membrane Builder

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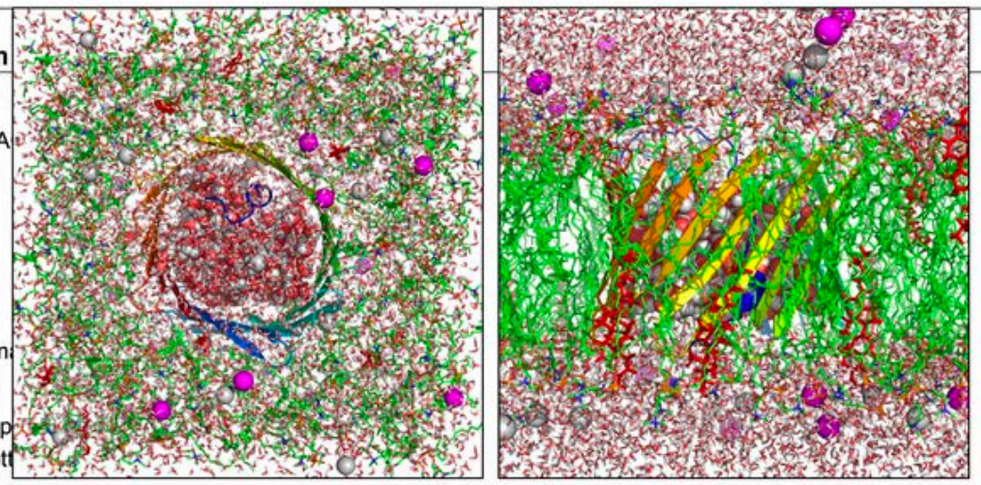
Determined System



# of Atoms		
Crystal Type	TETRA	
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	Gamm	
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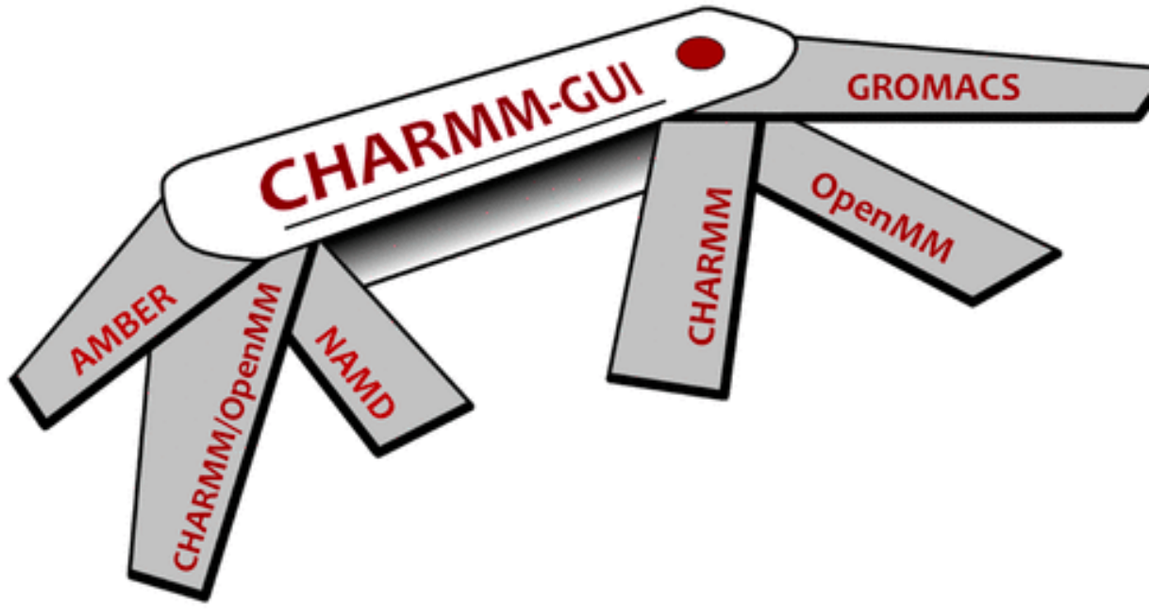

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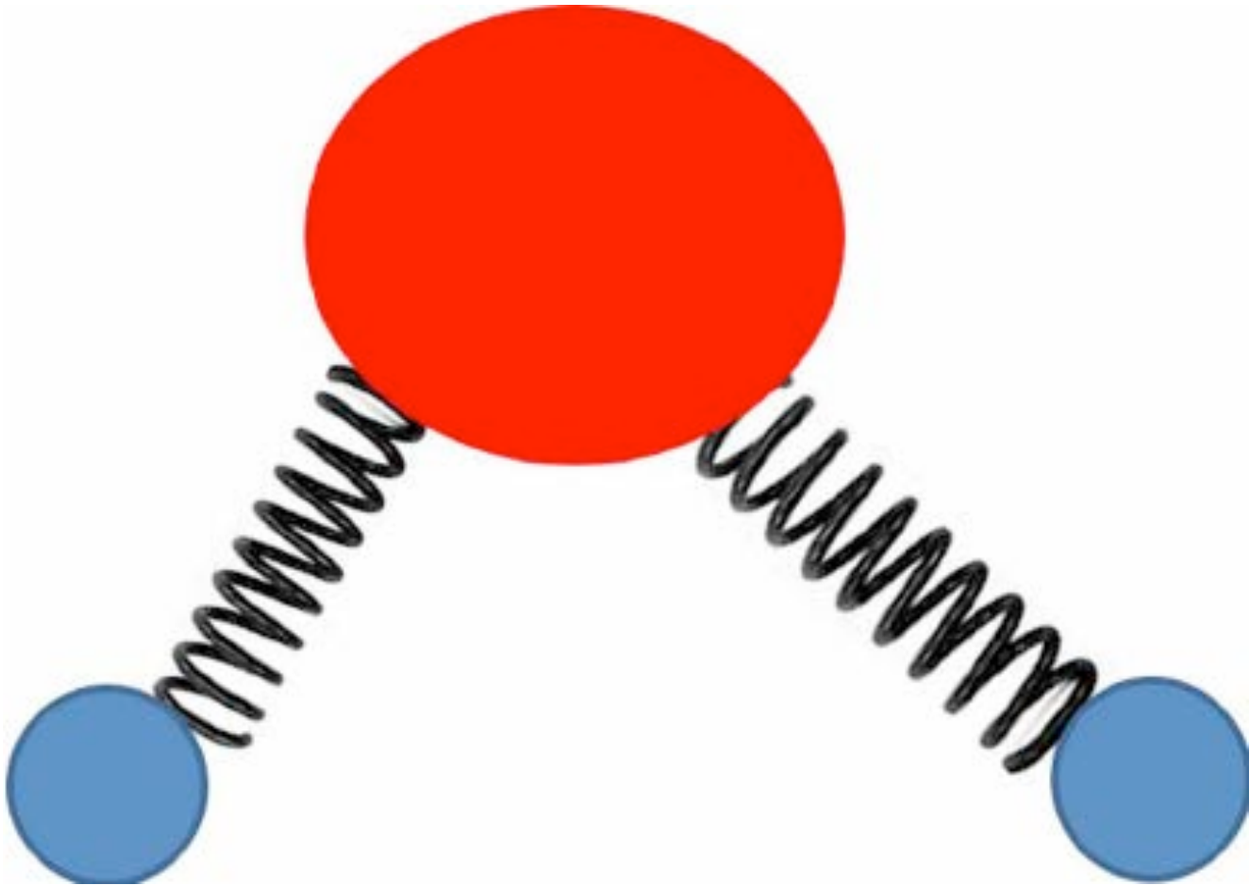
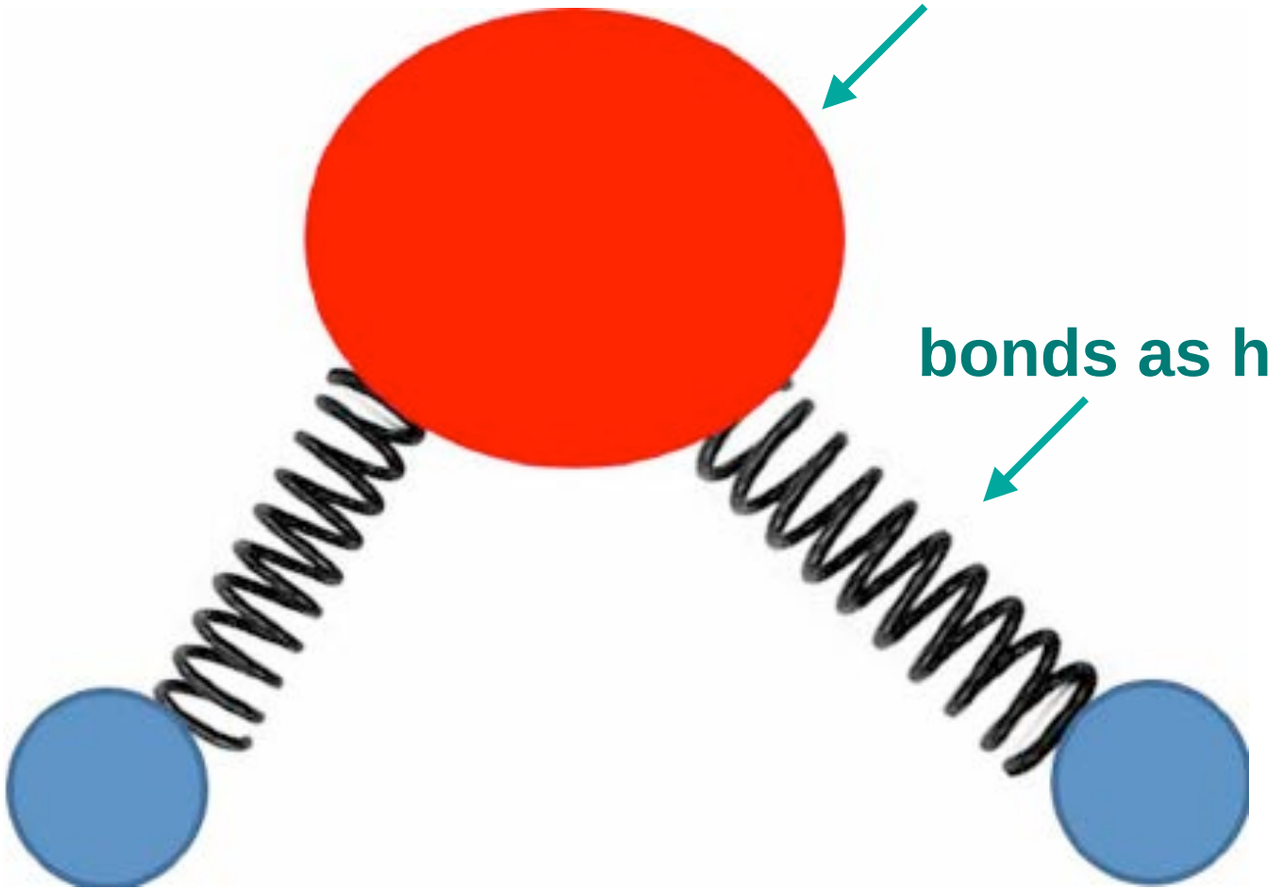
MD simulations is based on classical mechanic



Priya et al, Biomedical Image Analysis and Mining Techniques for Improved Health Outcomes, 2016

MD simulations is based on classical mechanic



Priya et al, Biomedical Image Analysis and Mining Techniques for Improved Health Outcomes, 2016

MD simulations: different levels of description

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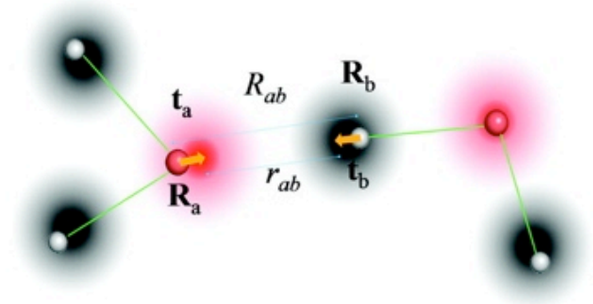
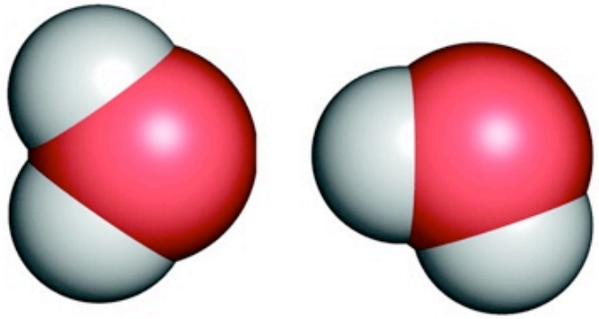
MD simulations: different levels of description

Quantum mechanics

$$\frac{-\hbar^2}{2m}\nabla^2\Psi(\mathrm{r}) + V(r)\Psi(\mathrm{r}) = E\Psi(\mathrm{r})$$

Kinetic Energy + *Potential Energy* = *Total Energy*





Donchev, PNAS, 2005

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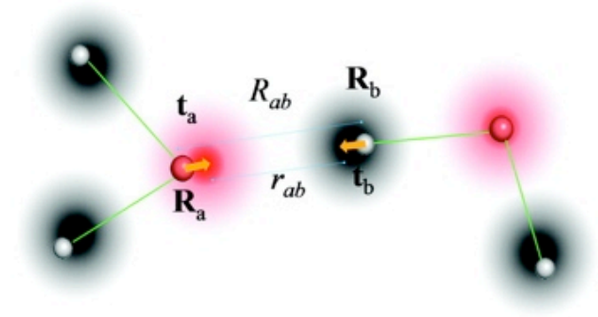

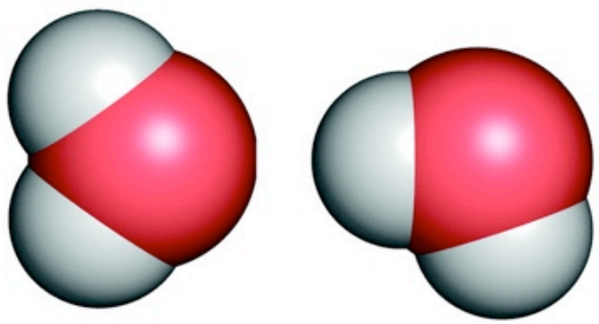

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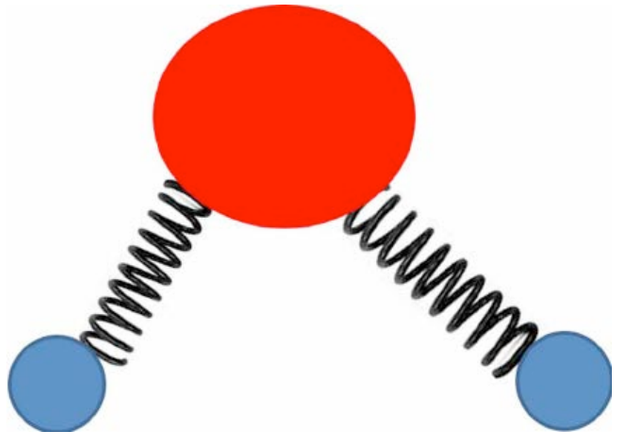
Priya et al, Biomedical Image Analysis and Mining Techniques for Improved Health Outcomes, 2016



Classical potential energy function:

Molecular mechanic (MM)

MD simulations: different levels of description

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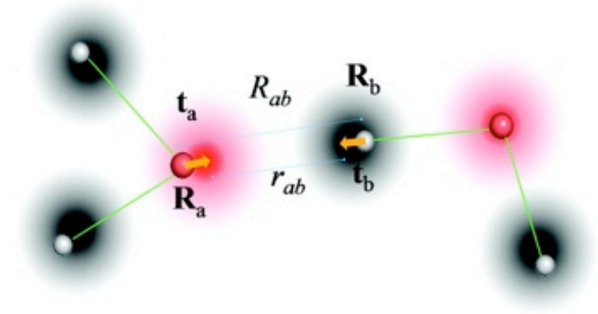
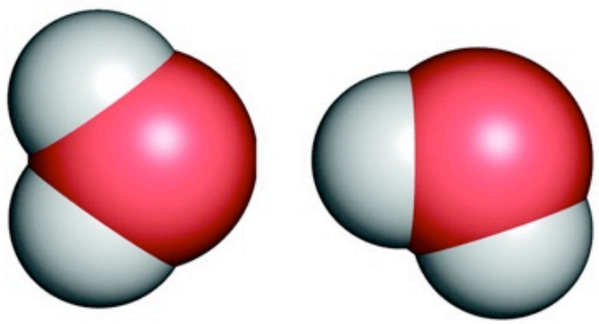
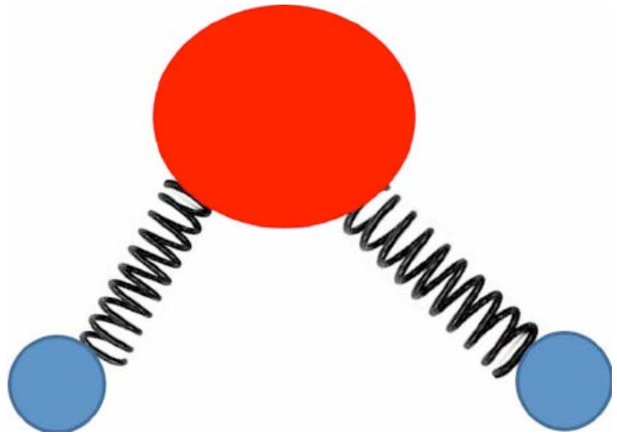




Donchev, PNAS, 2005

Priya et al, Biomedical Image Analysis and Mining Techniques for Improved Health Outcomes, 2016



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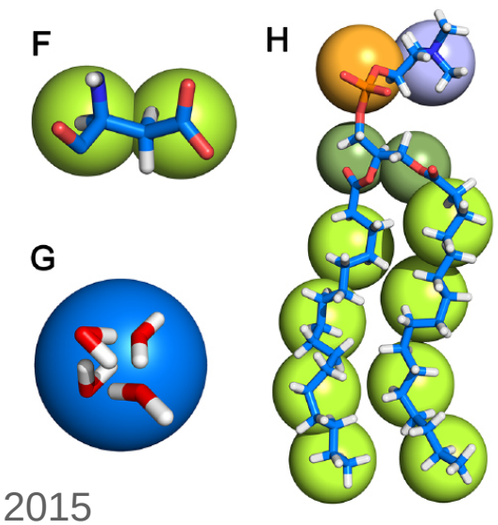

Pluhackova & Böckmann, J Phys, 2015

Coarse-grained modelling

MD simulations: different levels of description

Quantum mechanics

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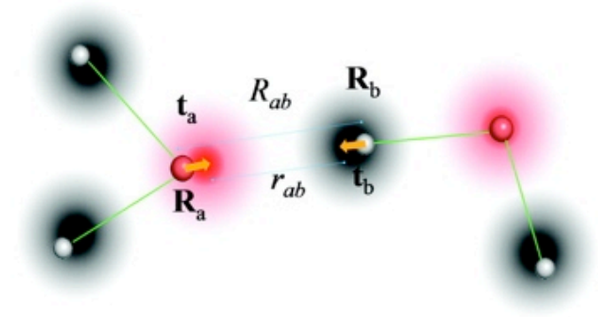
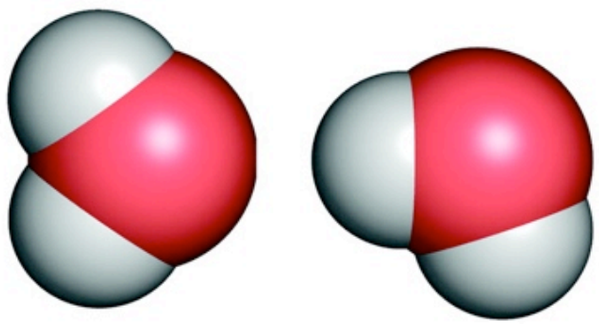


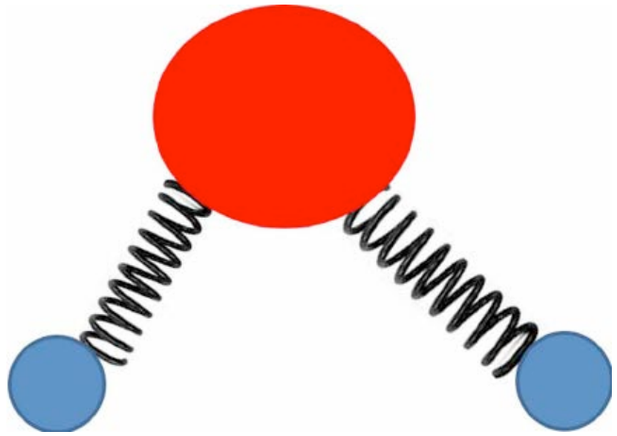


Donchev, PNAS, 2005

Combining is possible (multi-scaling)

Like QM and classical (QM/MM)

Priya et al, Biomedical Image Analysis and Mining Techniques for Improved Health Outcomes, 2016



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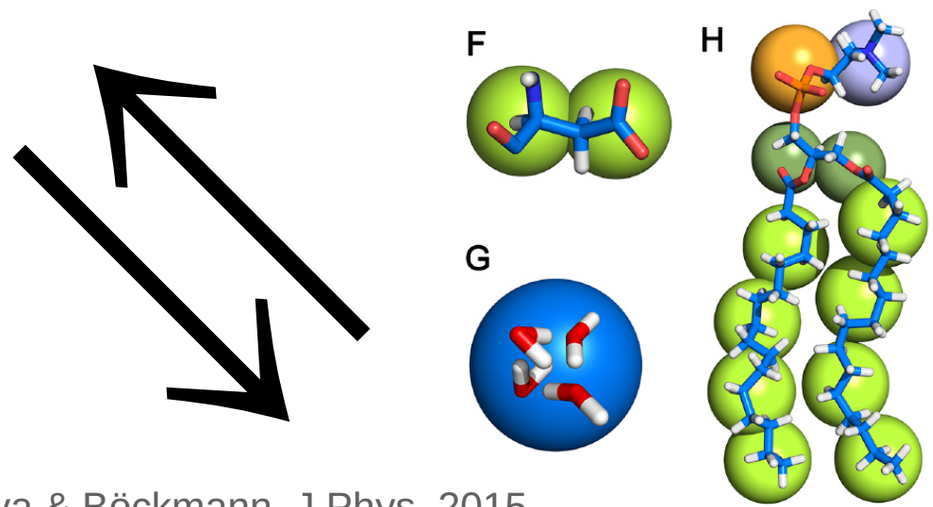

Pluhackova & Böckmann, J Phys, 2015

Coarse-grained modelling

Applications in molecular membrane biology

Ion/substrate binding	Protein-lipid interaction
Conformational change	Protein-protein interaction Post-translational modifications

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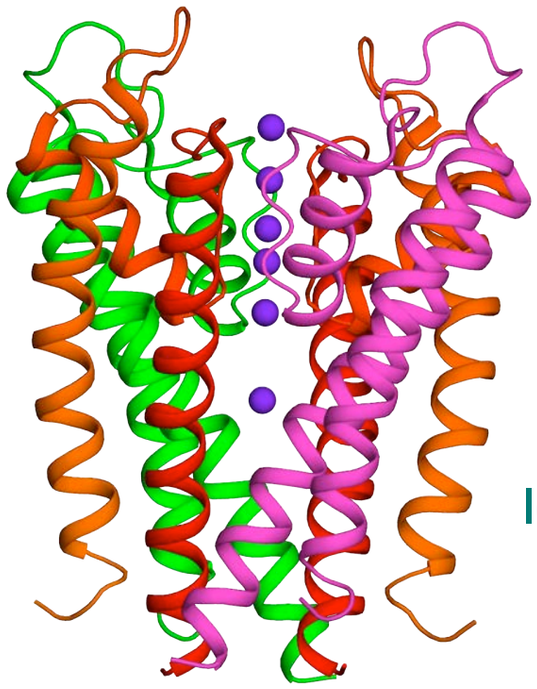
Applications in molecular membrane biology



Ion/substrate binding

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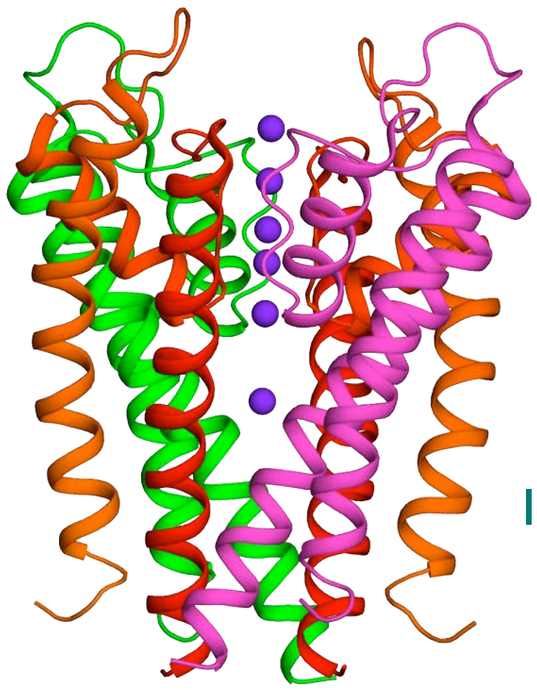
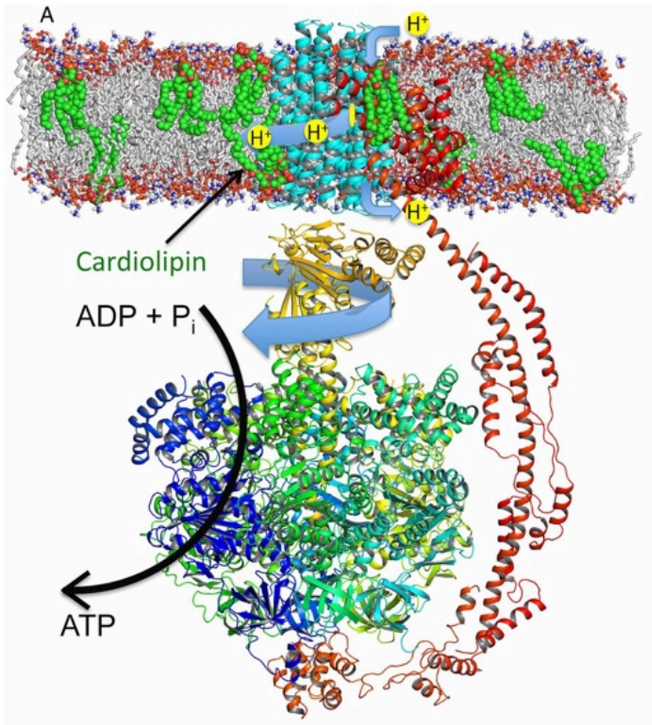
Applications in molecular membrane biology



Ion/substrate binding

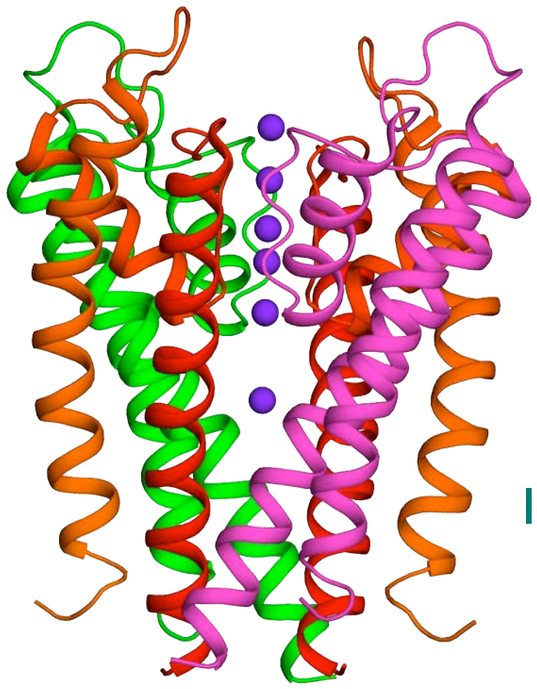
Protein-lipid interaction



Conformational change

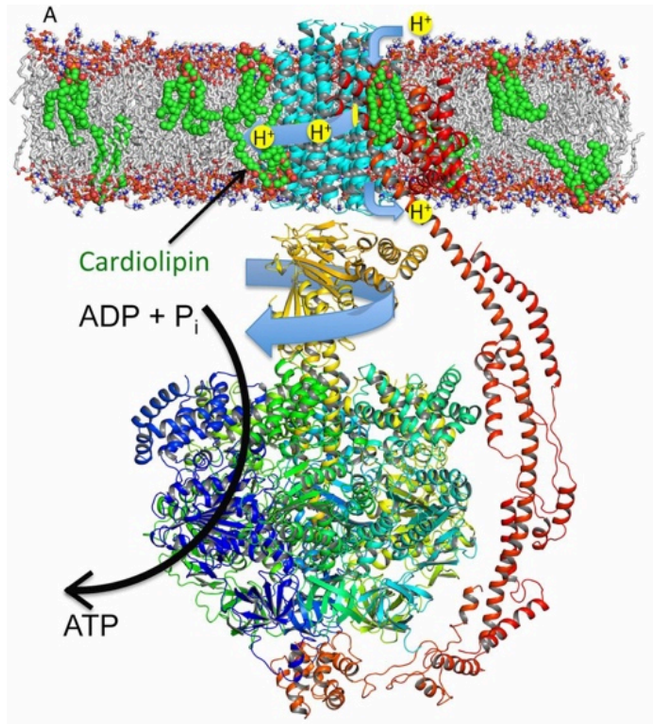
Protein-protein interaction
Post-translational modifications

Applications in molecular membrane biology



Ion/substrate binding

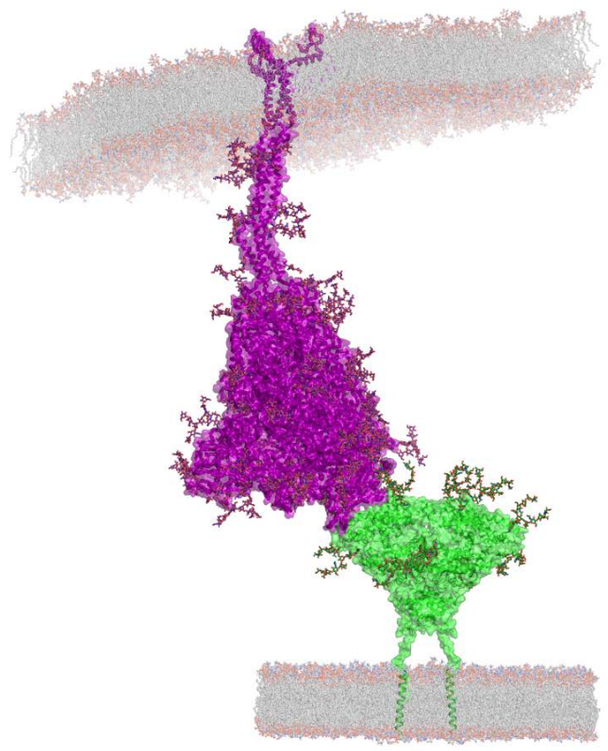
Protein-lipid interaction



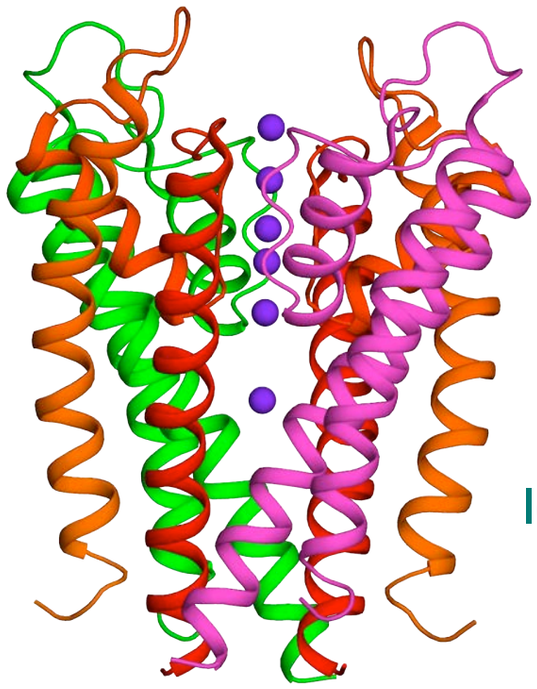
Conformational change

Protein-protein interaction

Post-translational modifications



Applications in molecular membrane biology



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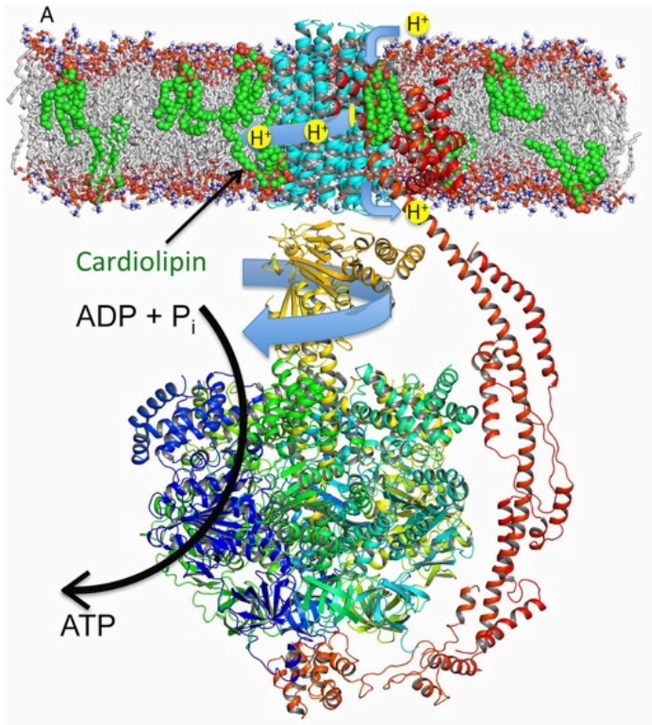

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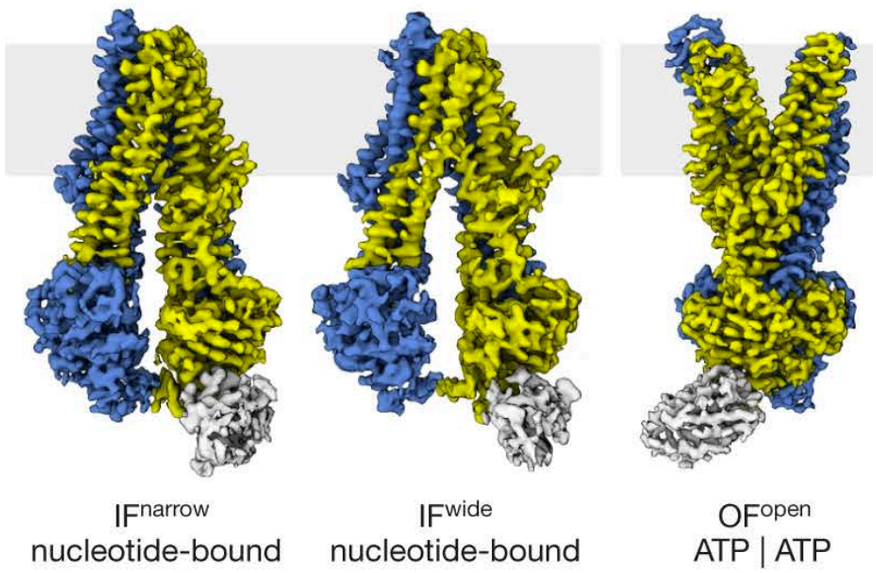
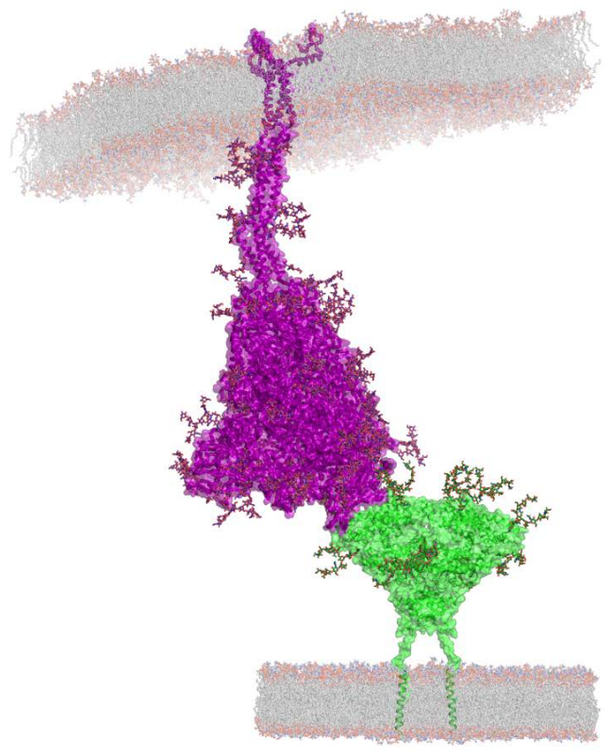
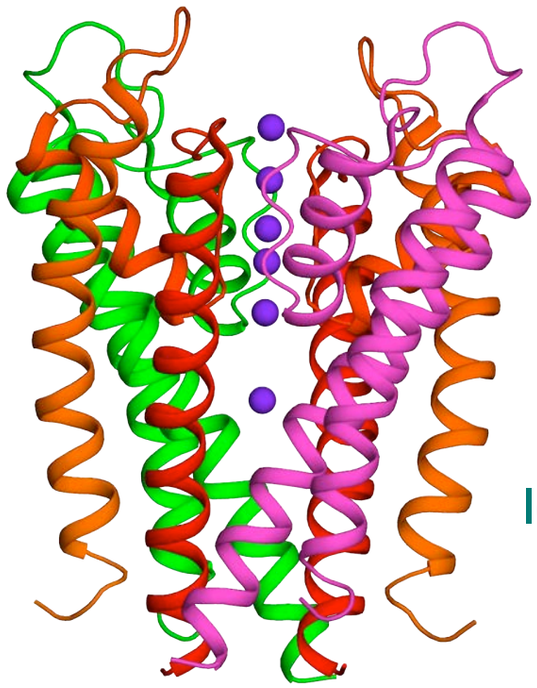


Protein-protein interaction
Post-translational modifications



Applications in molecular membrane biology



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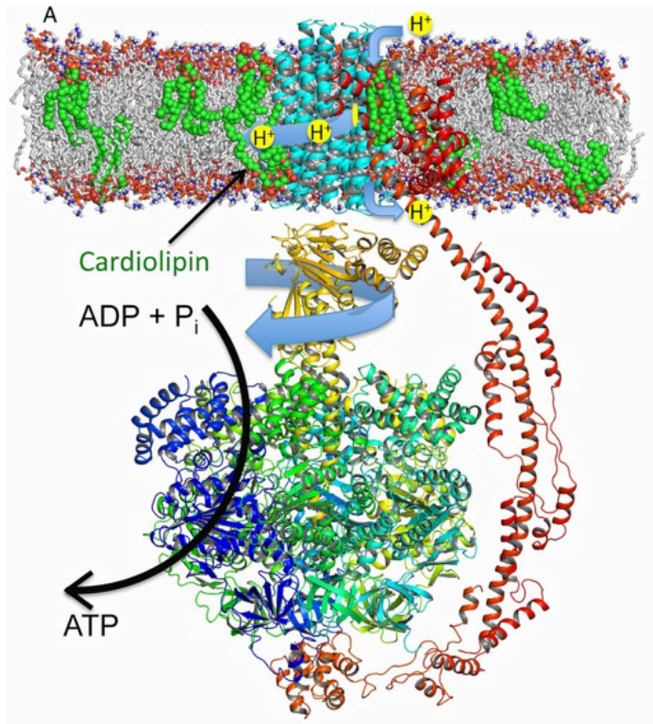

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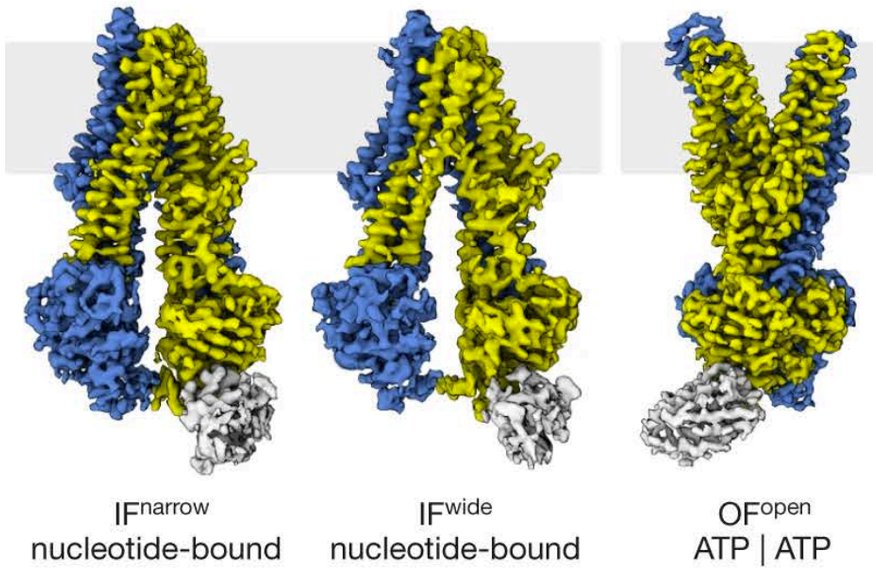
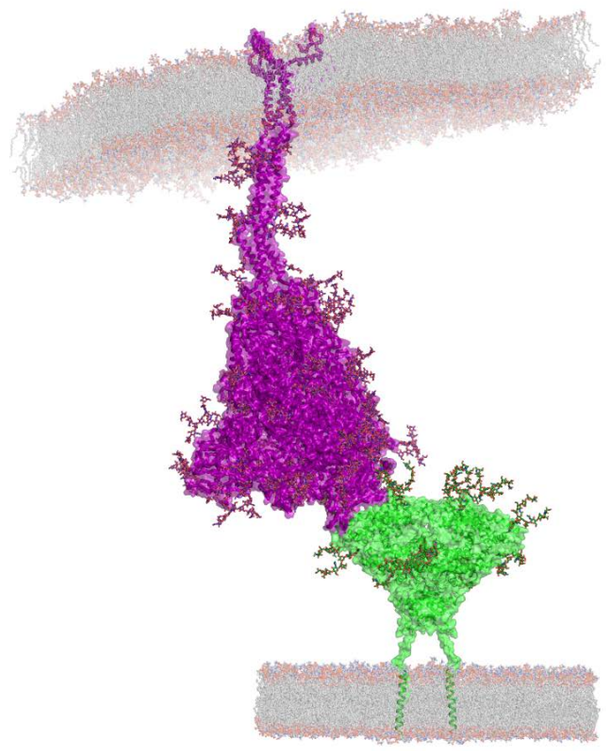
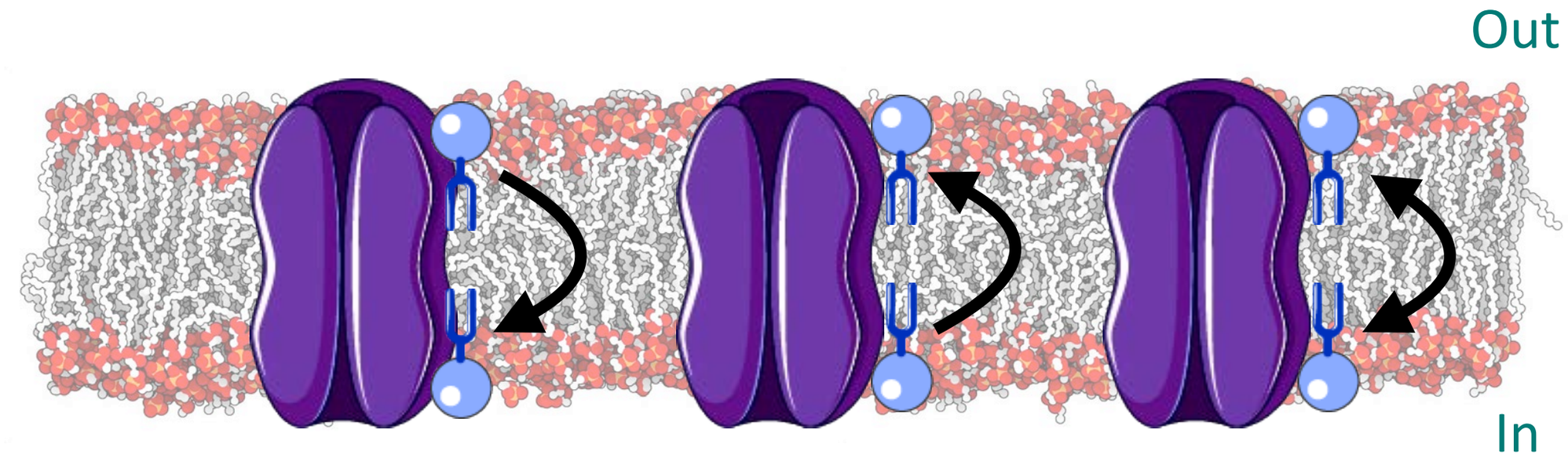


Protein-protein interaction
Post-translational modifications



Lipid movement across biological membranes

Active **Passive**



Flippase **Floppase** **Scramblase**

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Mechanisms of Flipping lipids

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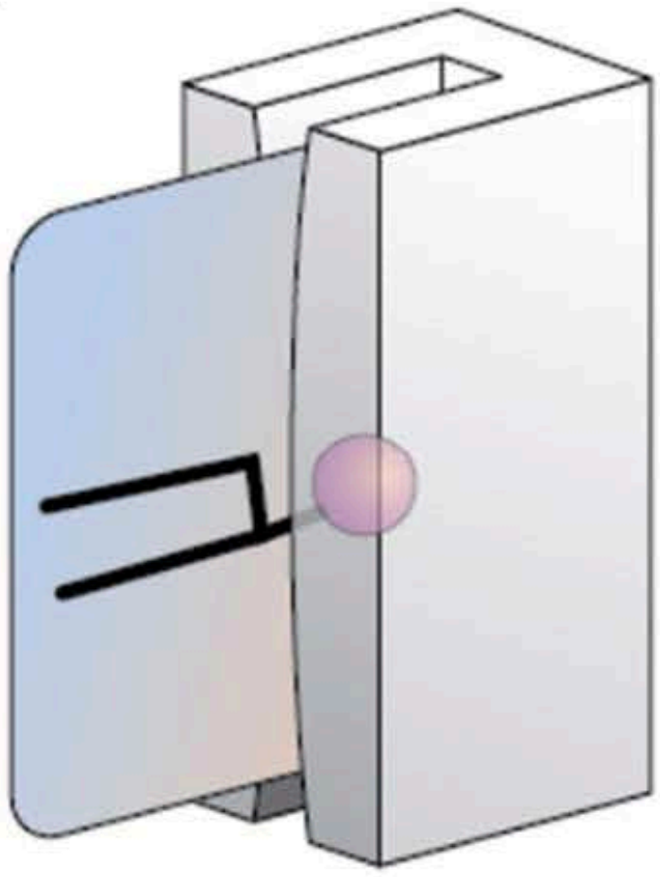
Mechanisms of Flipping lipids

Credit card



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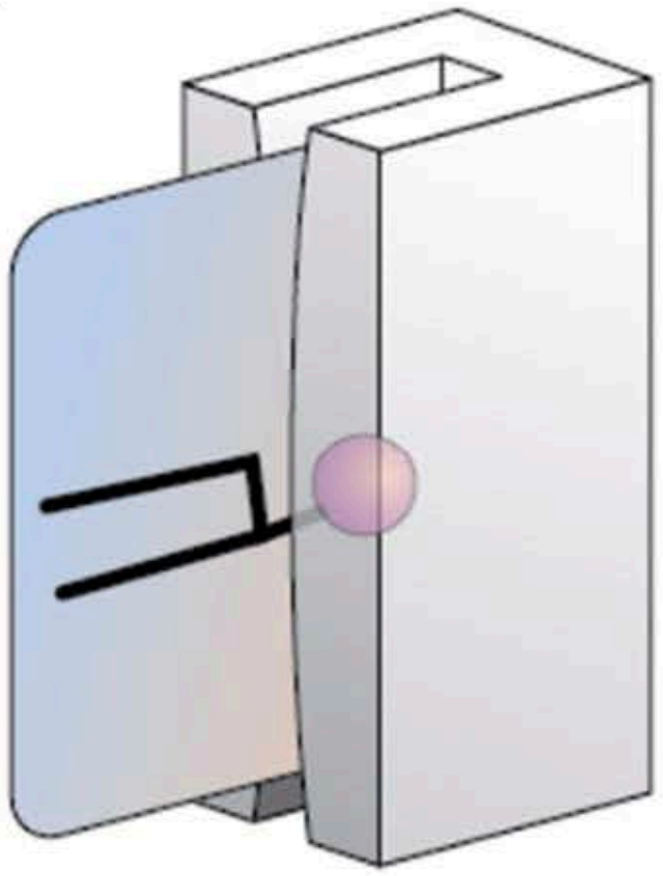
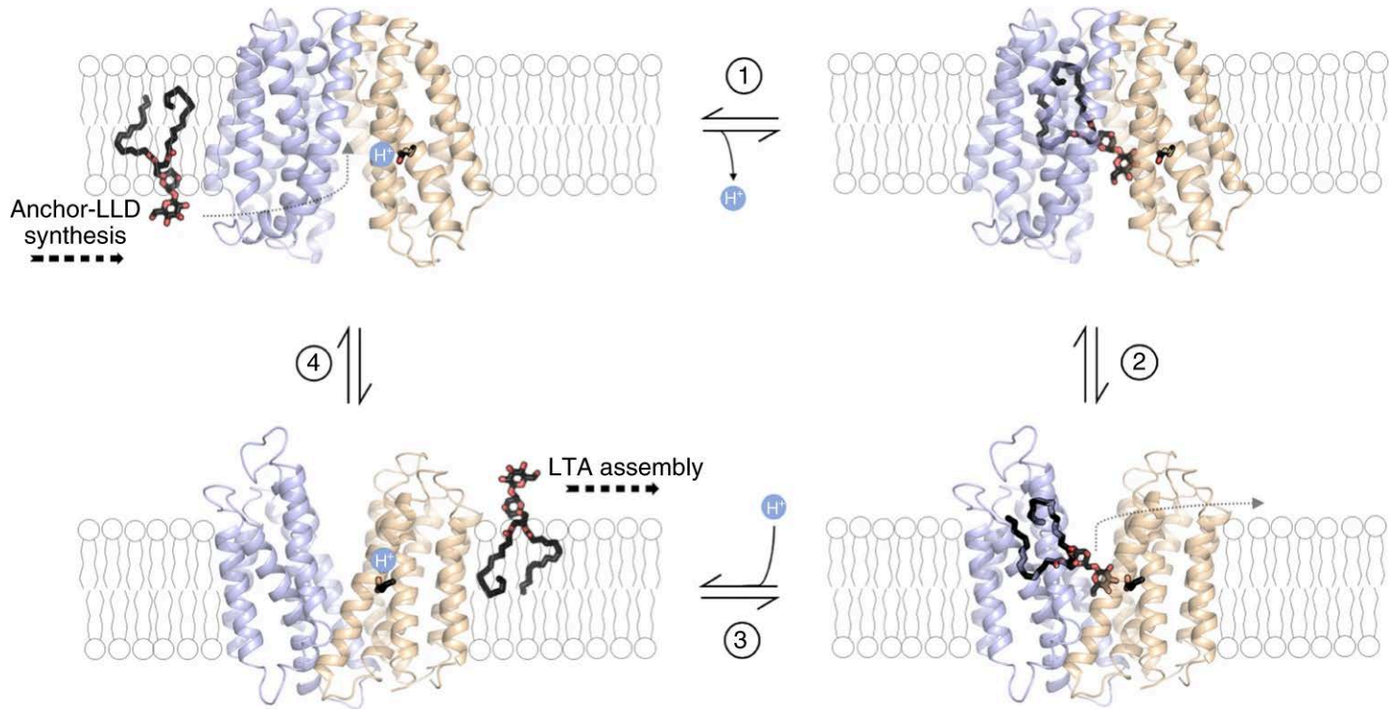
Mechanisms of Flipping lipids

Credit card



Trap-and-flip



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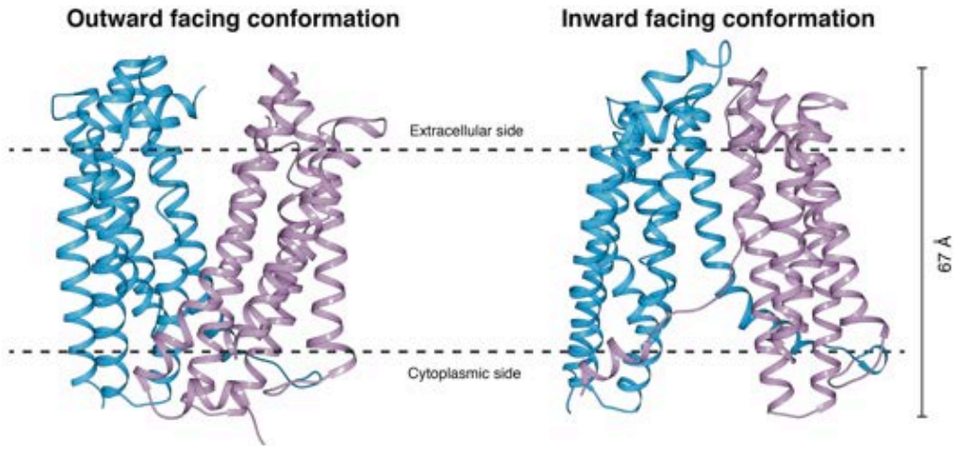
PfMATE

Hartmut Michel

Sandra Zakrzewska



Zakrzewska, Mehdipour, ..., Hummer, Safarian, Michel. PNAS, 2019

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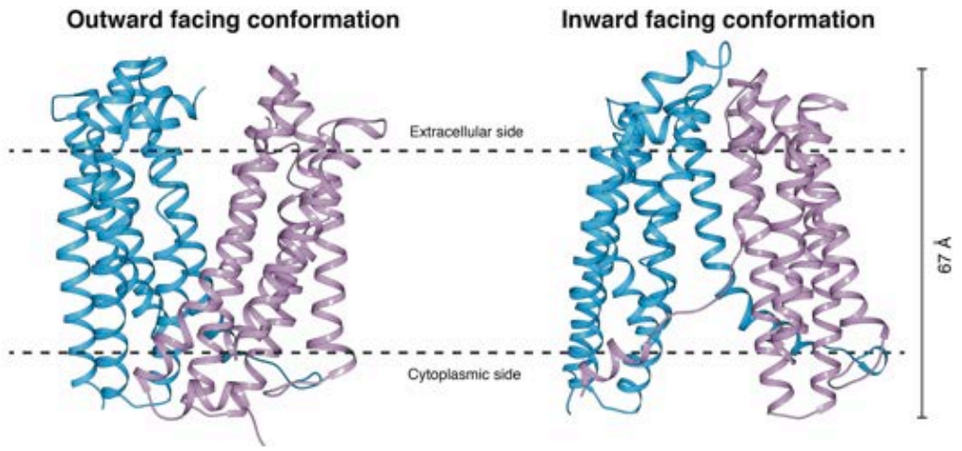

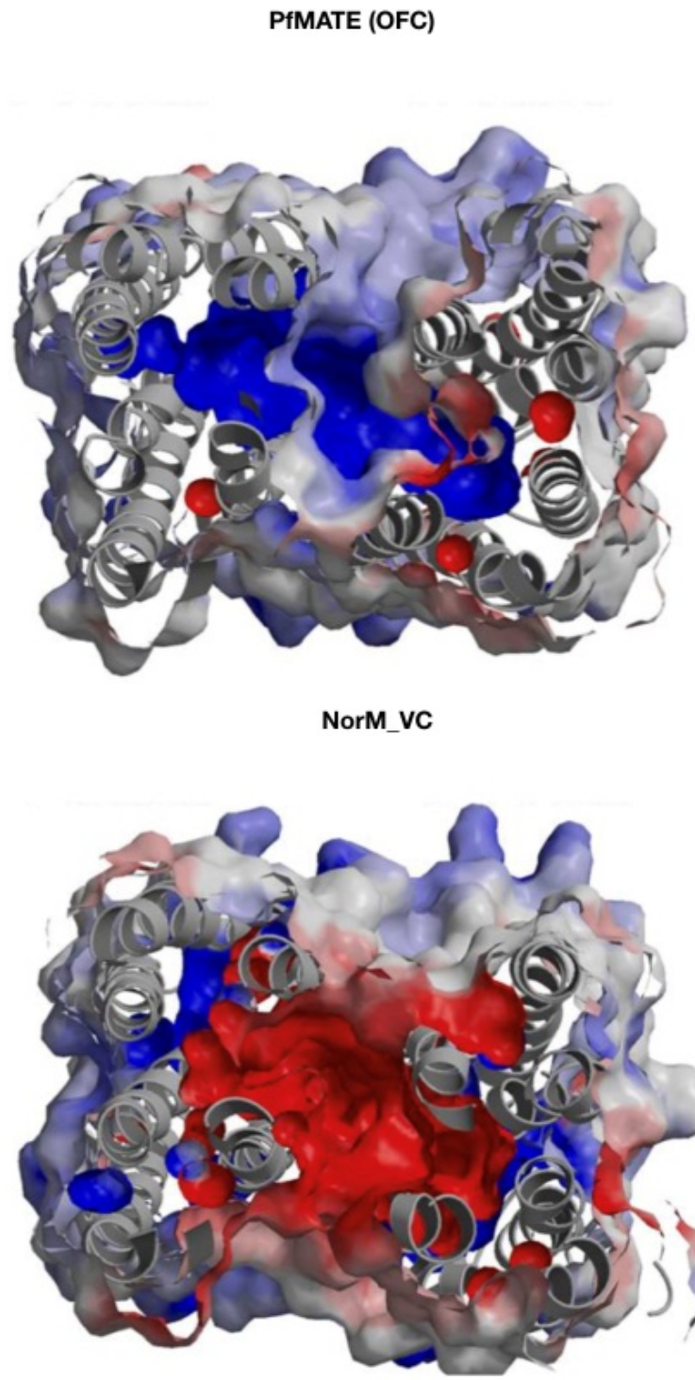

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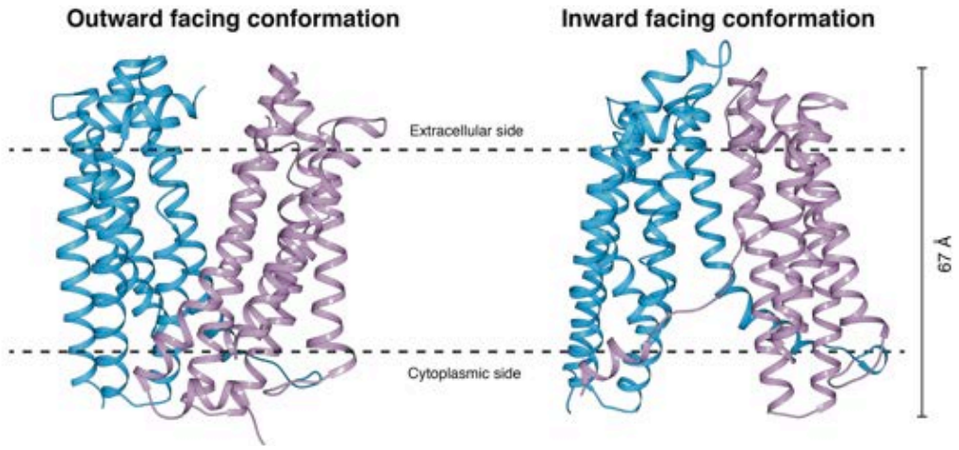
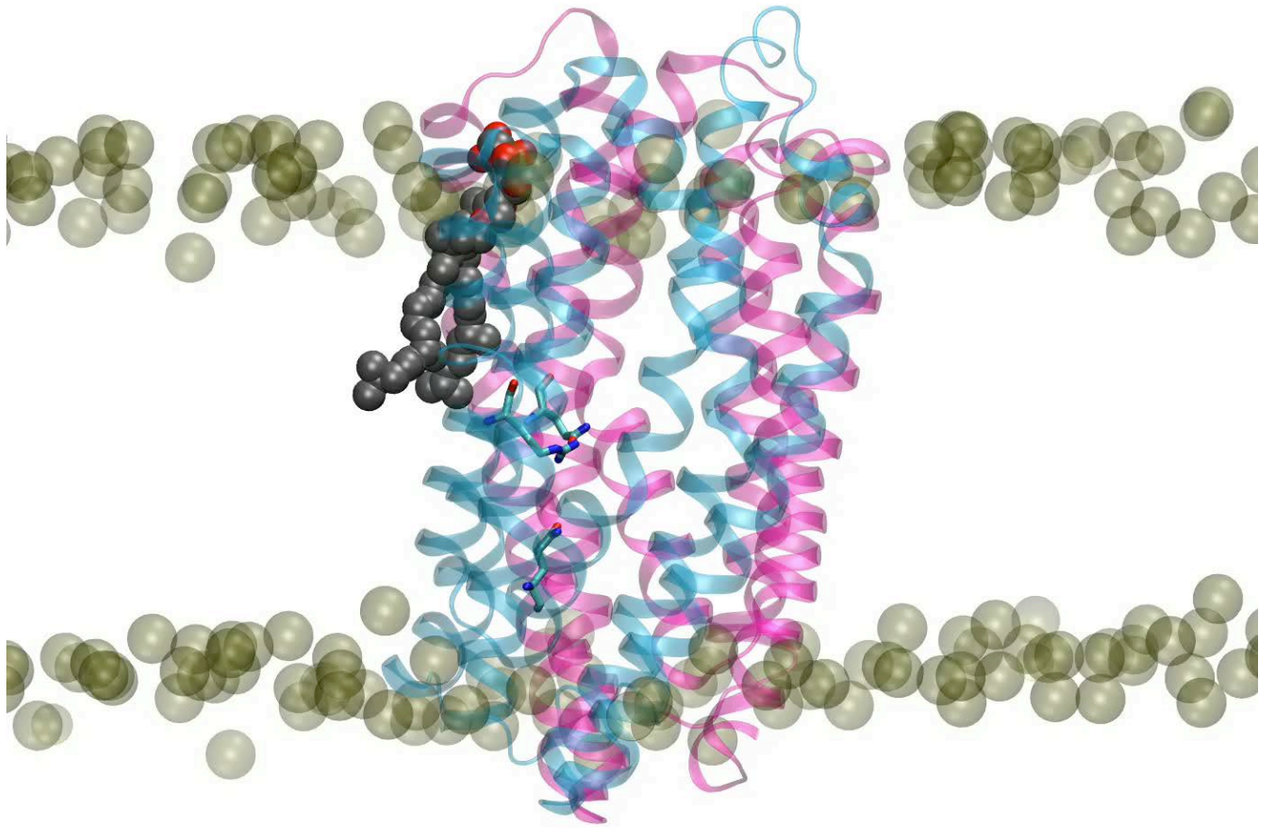
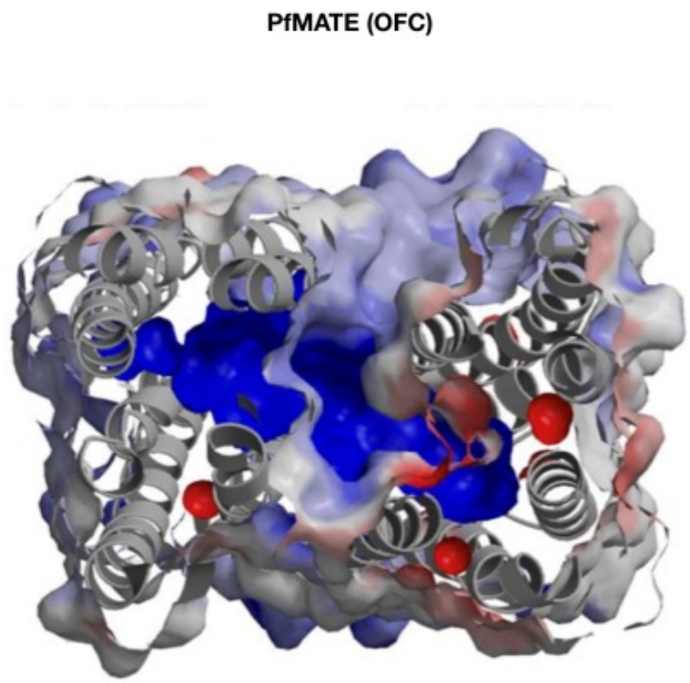
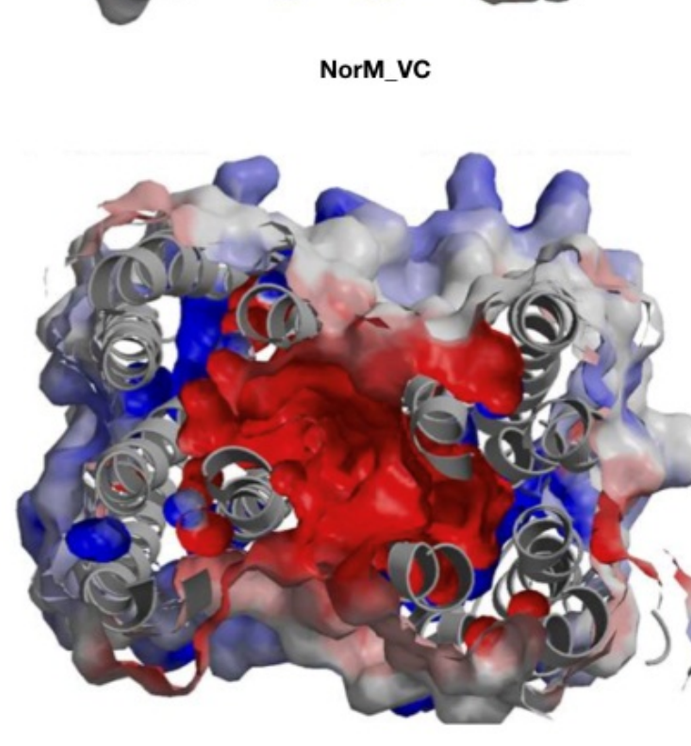


1.5 μs all-atom simulation of MATE transporter in an archaeal lipid bilayer







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Zakrzewska, Mehdipour, ..., Hummer, Safarian, Michel. PNAS, 2019

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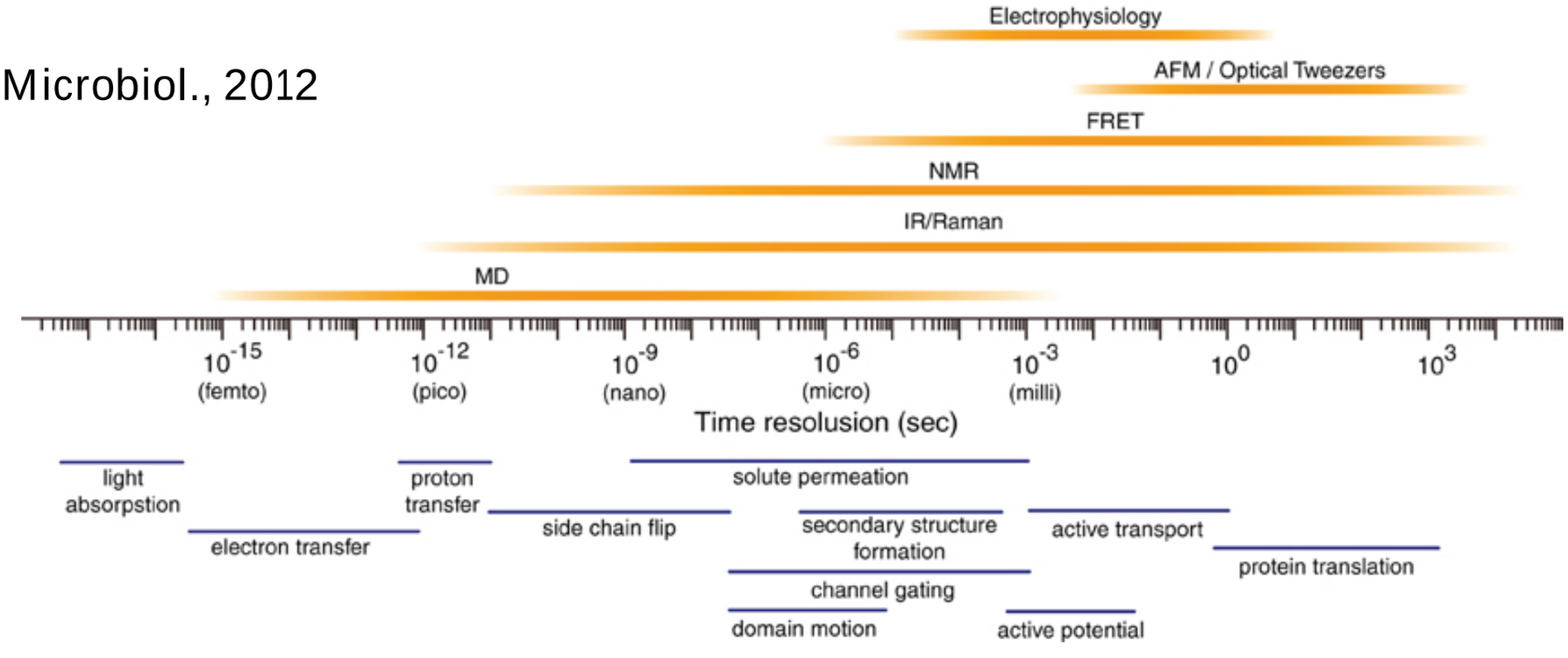
Outline

- Theoretical Biophysics
- Molecular dynamics (MD) simulations
- Applications of MD simulations in membrane biology
  - Protein-lipid interaction: lipid flippase
- **Advanced methods**
- Future directions

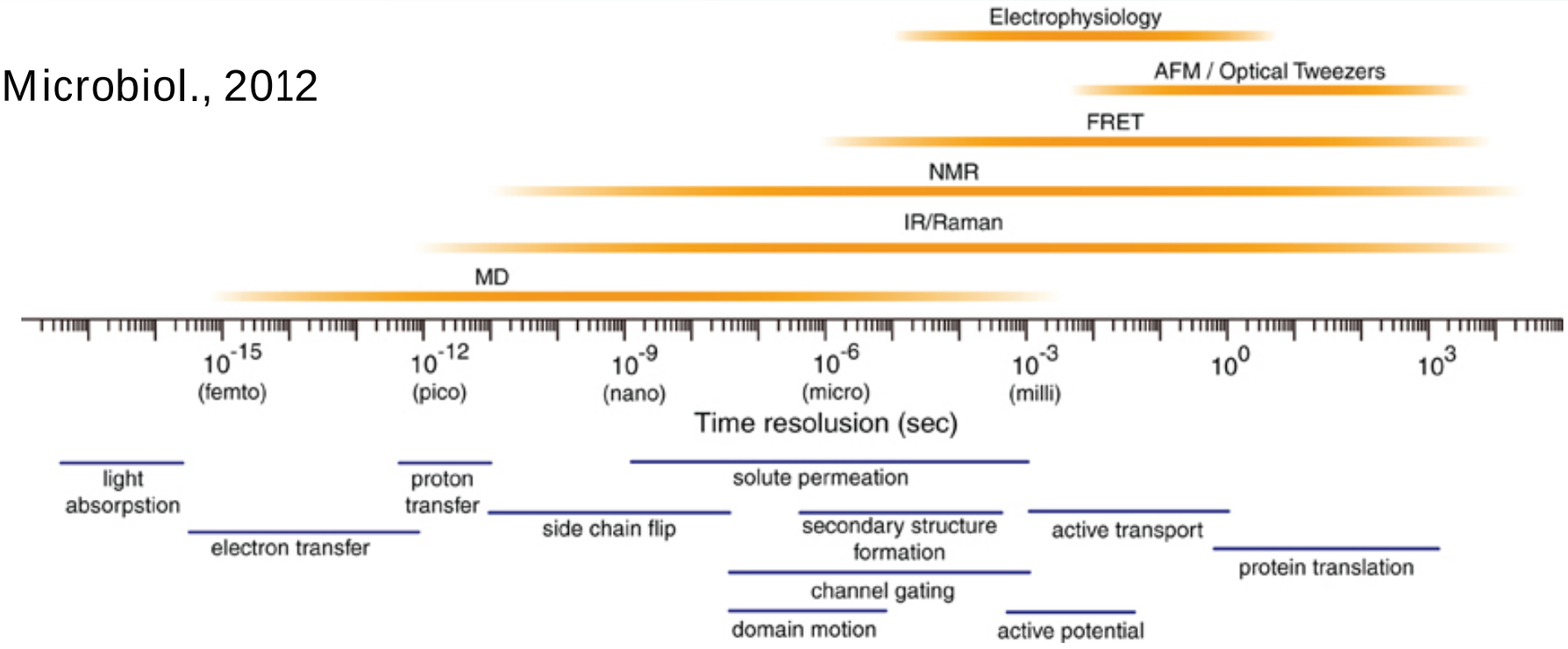
Time scale problem

Ode et al. Front. Microbiol., 2012

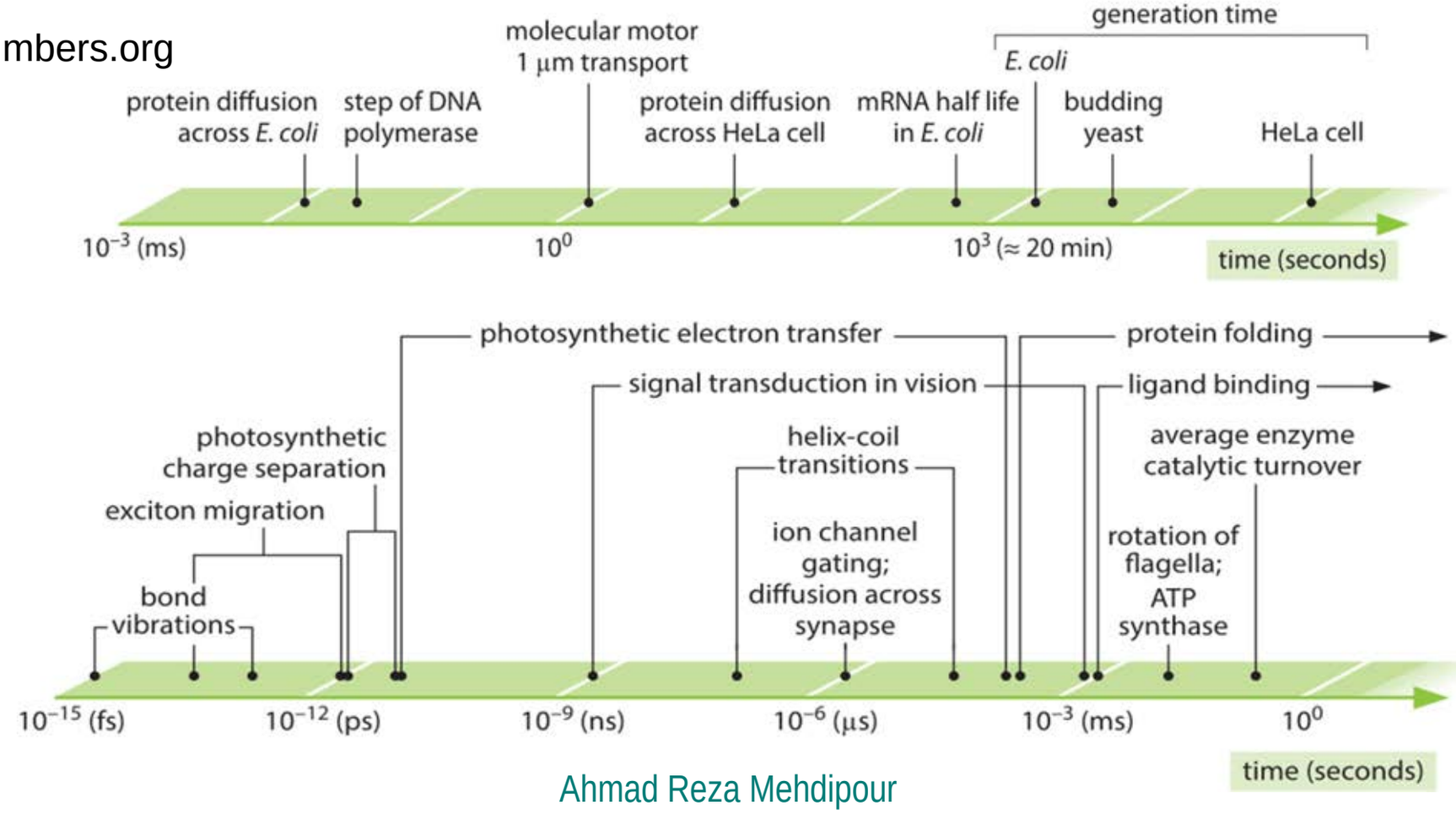


Time scale problem

Ode et al. Front. Microbiol., 2012



book.bionumbers.org



Time scale problem: solutions

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Time scale problem: solutions

Solutions

Time scale problem: solutions

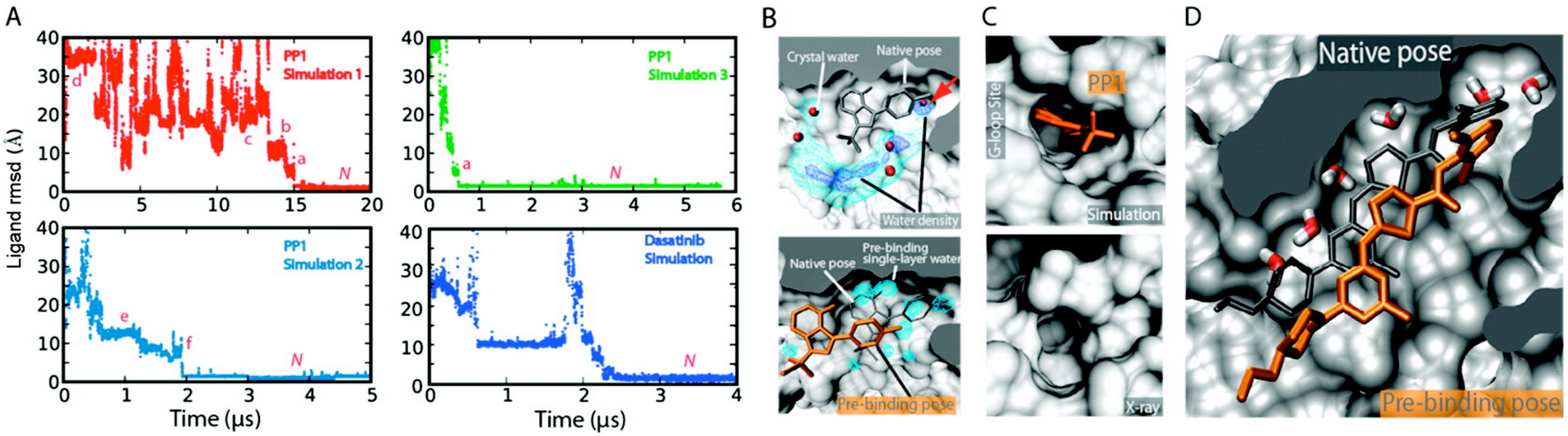
Solutions

★ Specialised MD supercomputers: Anton

Time scale problem: solutions

Solutions

★ Specialised MD supercomputers: Anton



Time scale problem: solutions

Solutions

★ Specialised MD supercomputers: Anton

★ Enhanced Sampling

Time scale problem: solutions

Solutions

★ Specialised MD supercomputers: Anton

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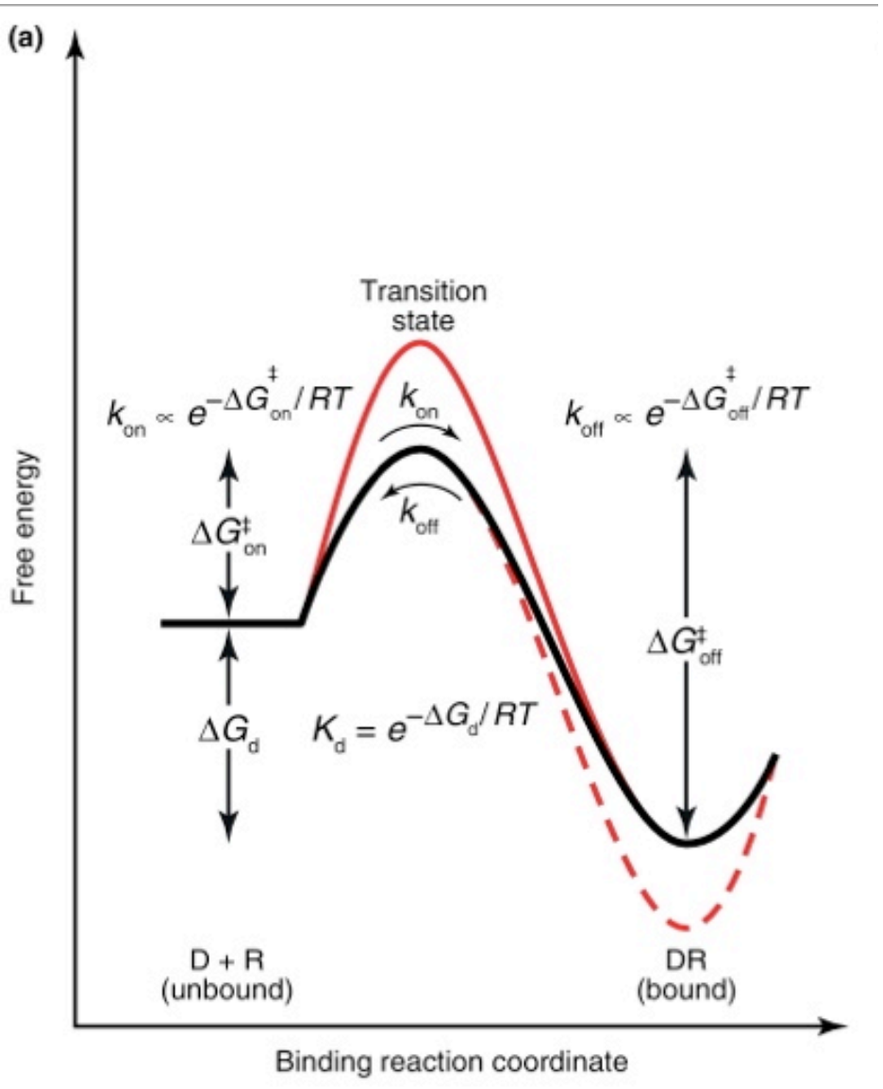

Time scale problem: solutions

Solutions

★ Specialised MD supercomputers: Anton

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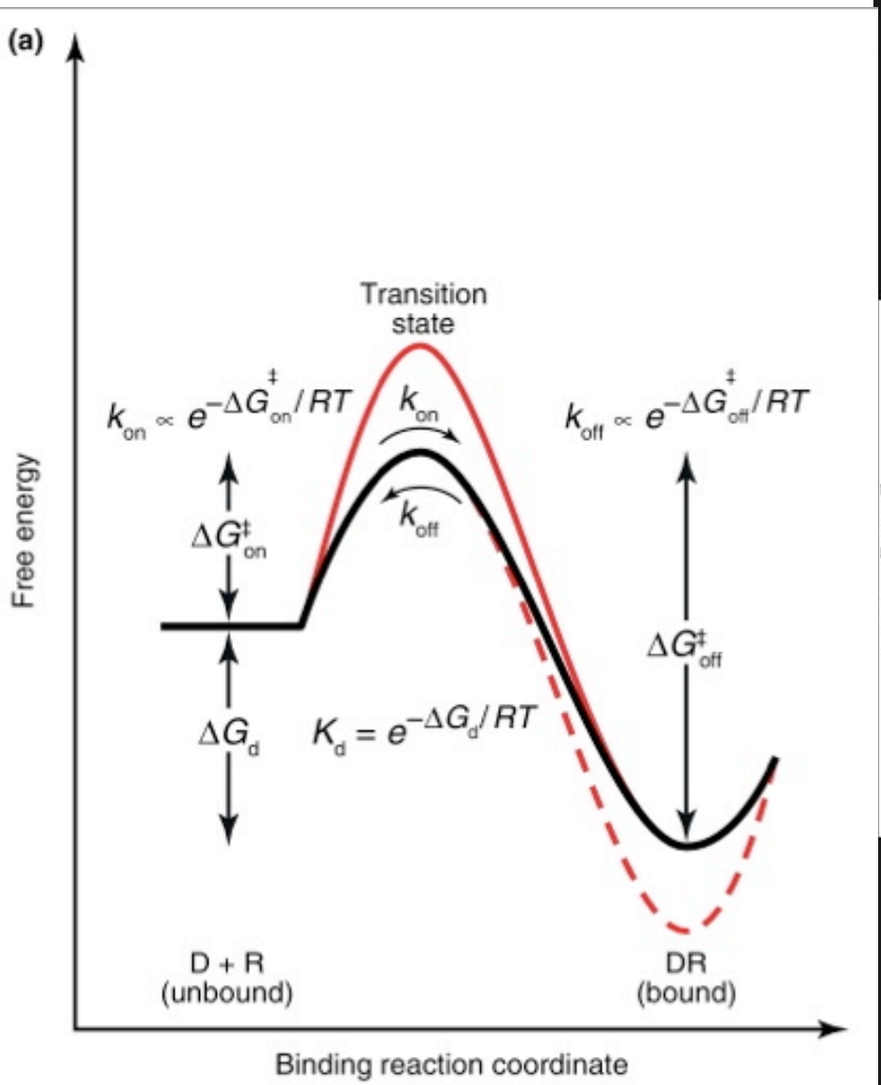

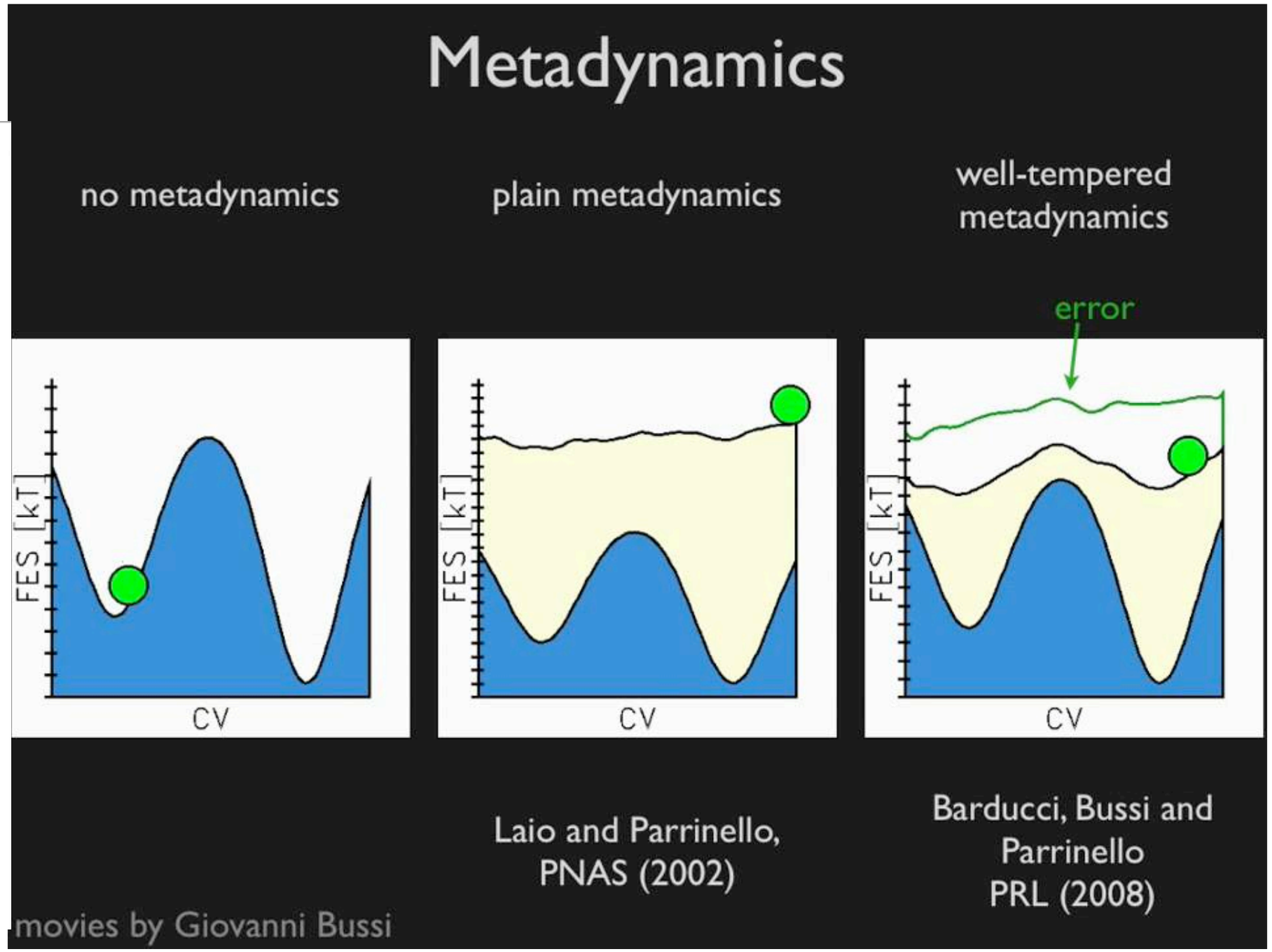

Outline

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Future: from molecular biology to cell biology

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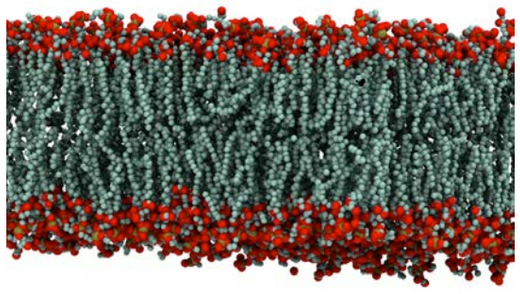
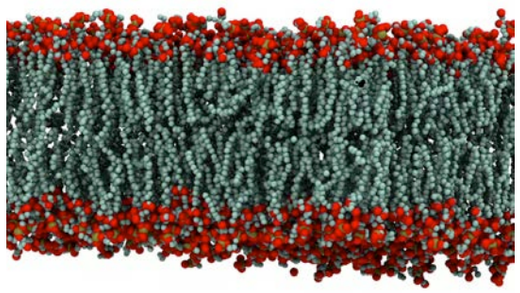
Future: from molecular biology to cell biology



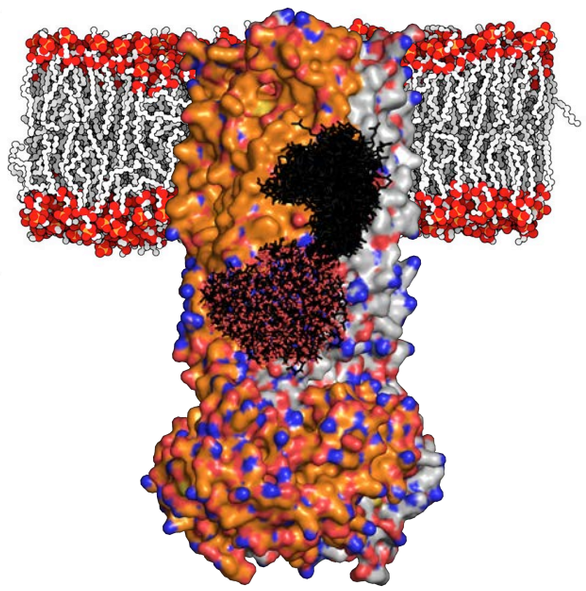
10×10×14 nm

~ 100,000 Atoms

Future: from molecular biology to cell biology

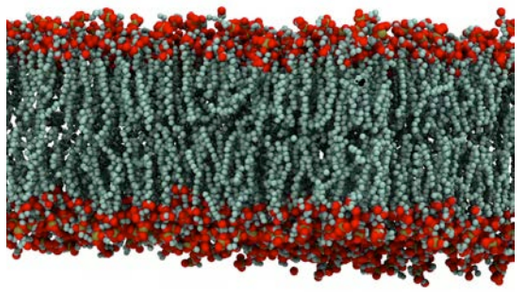


10×10×14 nm
~ 100,000 Atoms

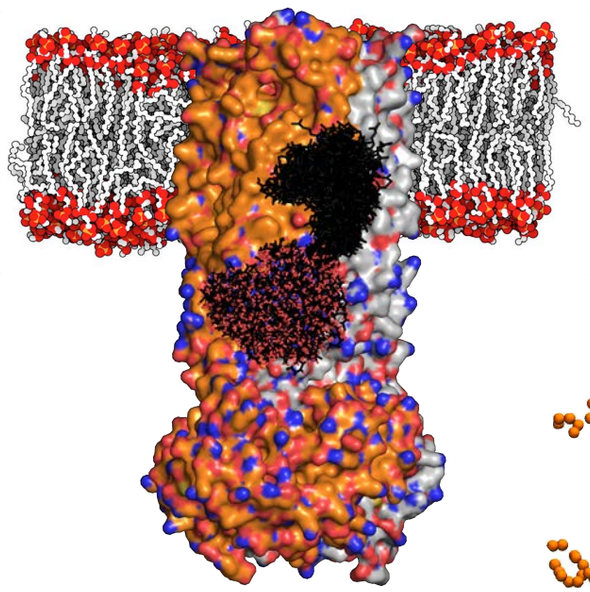


14×14×16 nm
~ 280,000 Atoms

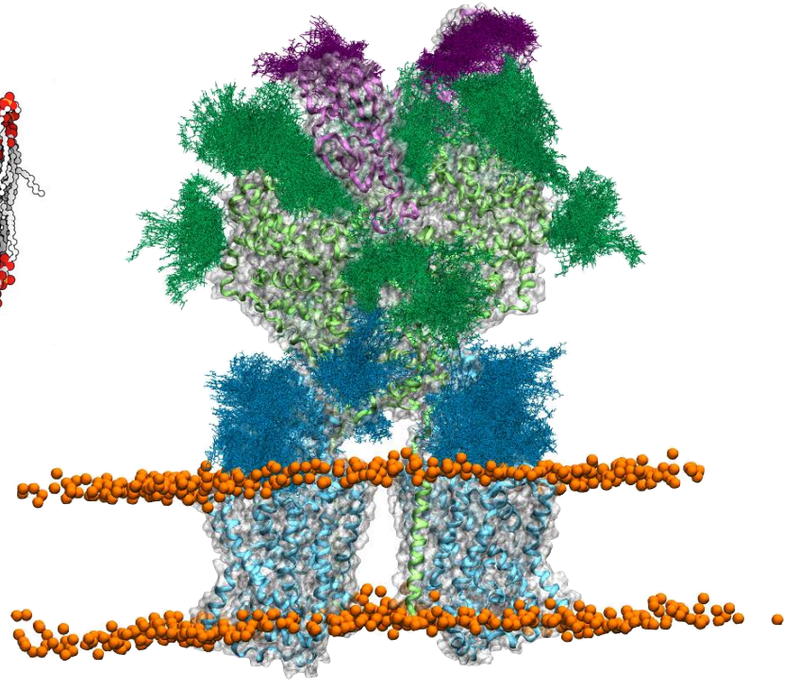
Future: from molecular biology to cell biology



10×10×14 nm
~ 100,000 Atoms

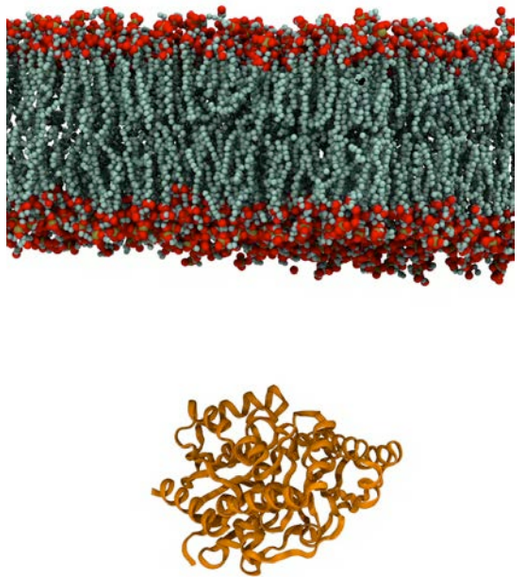


14×14×16 nm
~ 280,000 Atoms

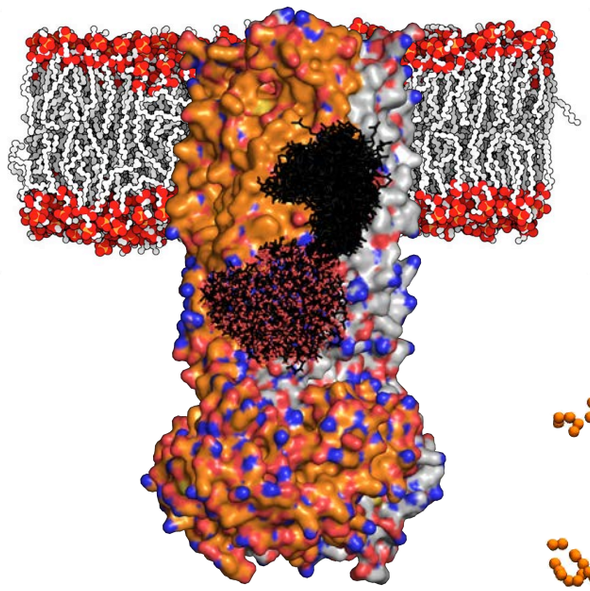


21×21×26 nm
~ 1,000,000 Atoms

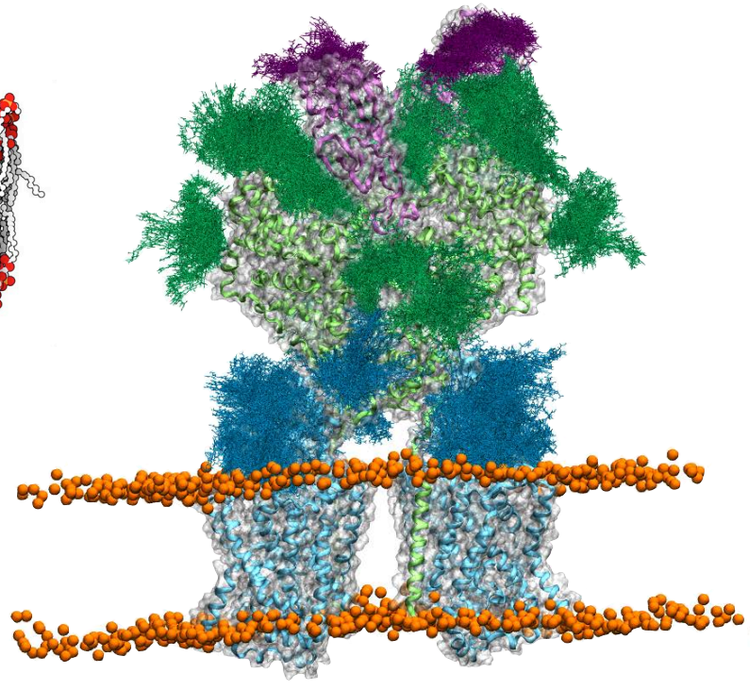
Future: from molecular biology to cell biology



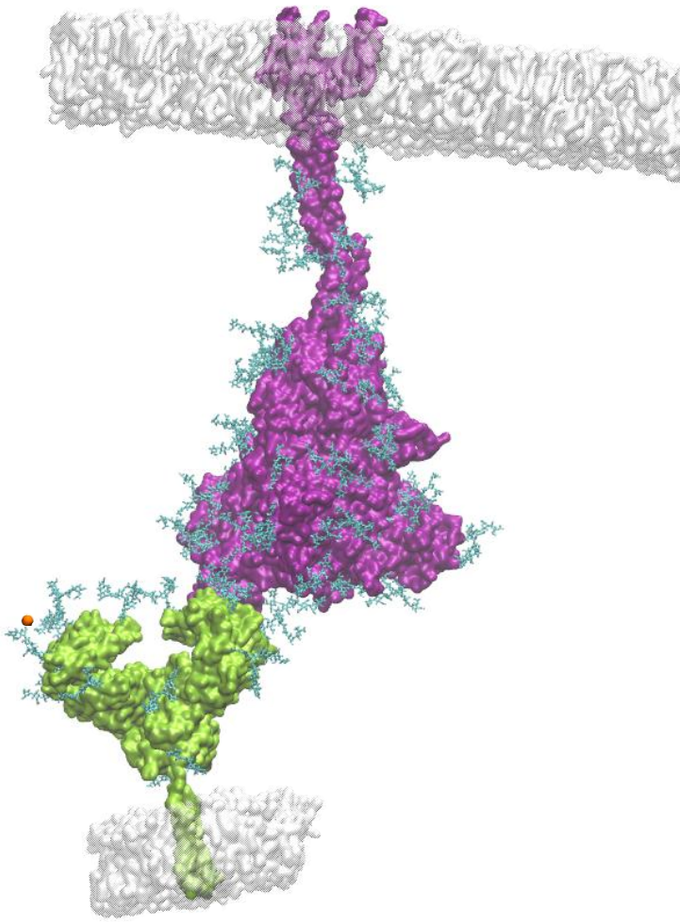
10×10×14 nm
~ 100,000 Atoms



14×14×16 nm
~ 280,000 Atoms

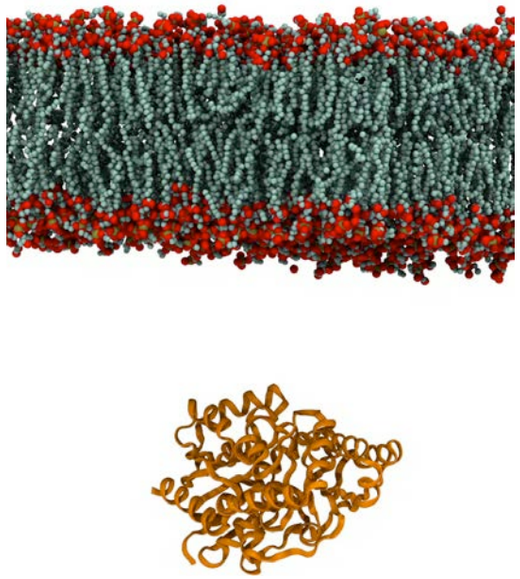


21×21×26 nm
~ 1,000,000 Atoms

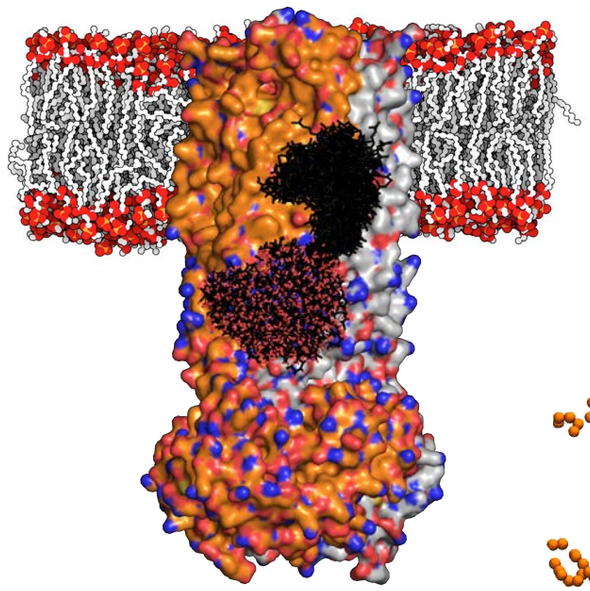


30×30×65 nm
~ 5,000,000 Atoms

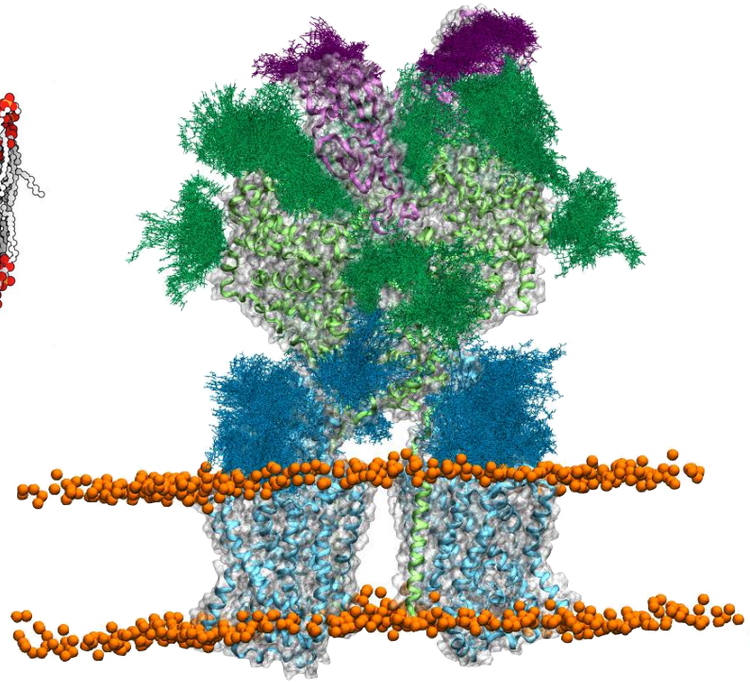
Future: from molecular biology to cell biology



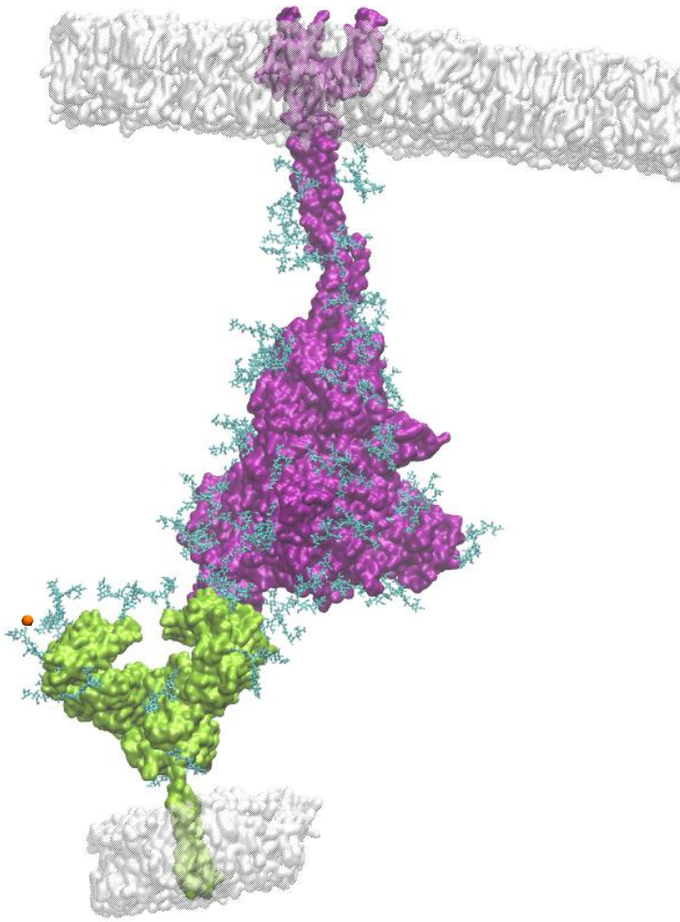
10×10×14 nm
~ 100,000 Atoms



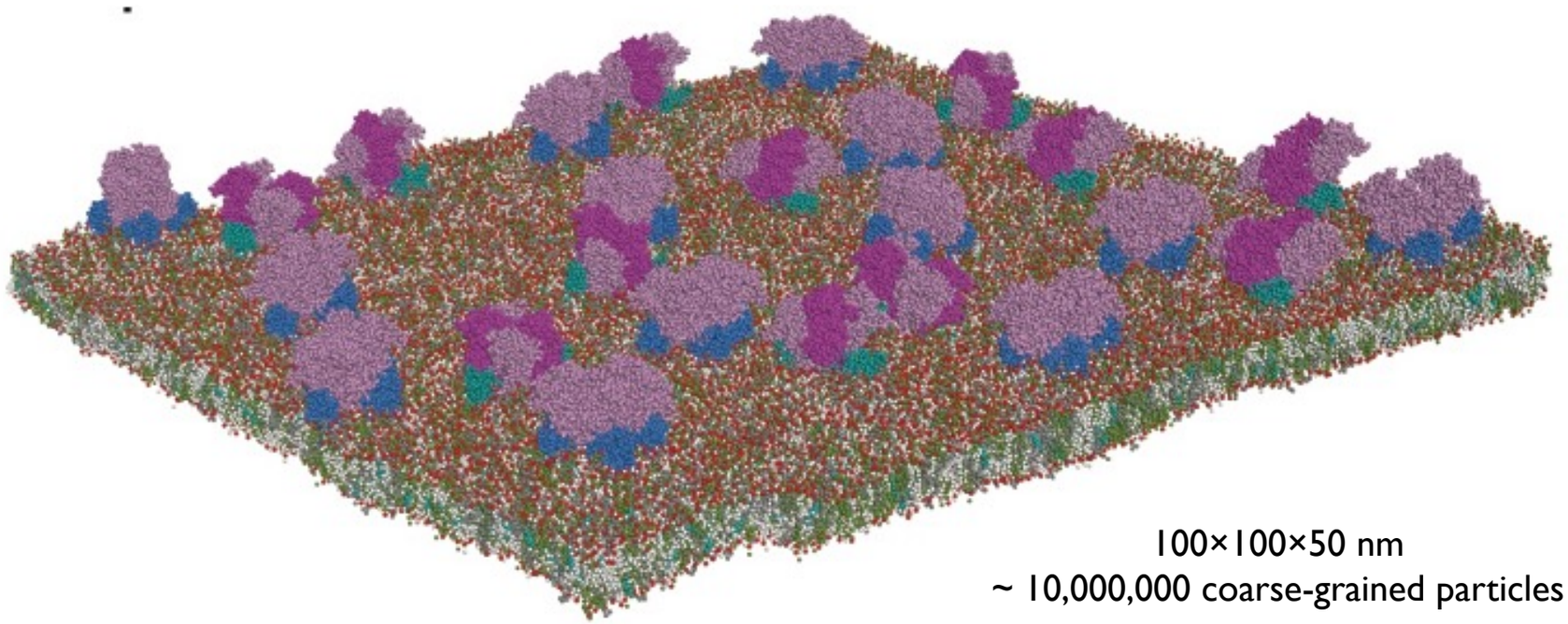
14×14×16 nm
~ 280,000 Atoms



21×21×26 nm
~ 1,000,000 Atoms

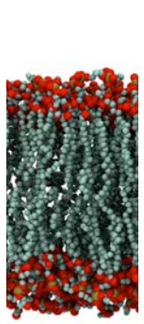


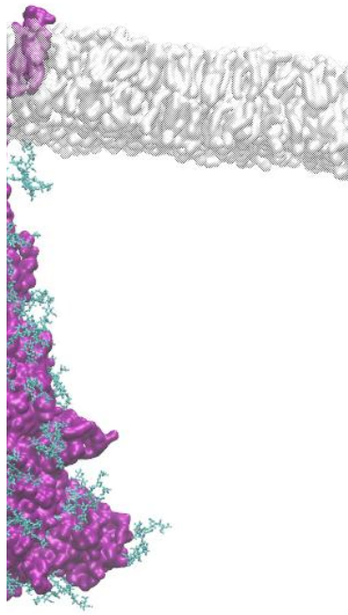
30×30×65 nm
~ 5,000,000 Atoms



100×100×50 nm
~ 10,000,000 coarse-grained particles

Future: from molecular biology to cell biology





Size of system

mm

µm

nm

pm

Coarse grained simulation

Mesoscale Properties

Protein folding, aggregation, polysaccharide fibre and biological assembly

All-atom based simulation

Conformational dynamics, loop movements and local motions.

Quantum

Mostly used to explore the chemical reactions and their mechanisms

fs ps ns µs ms s Time scale

65 nm
)0 Atoms

Singh & Li, IJMS, 2019

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Future: Alphafold and beyond

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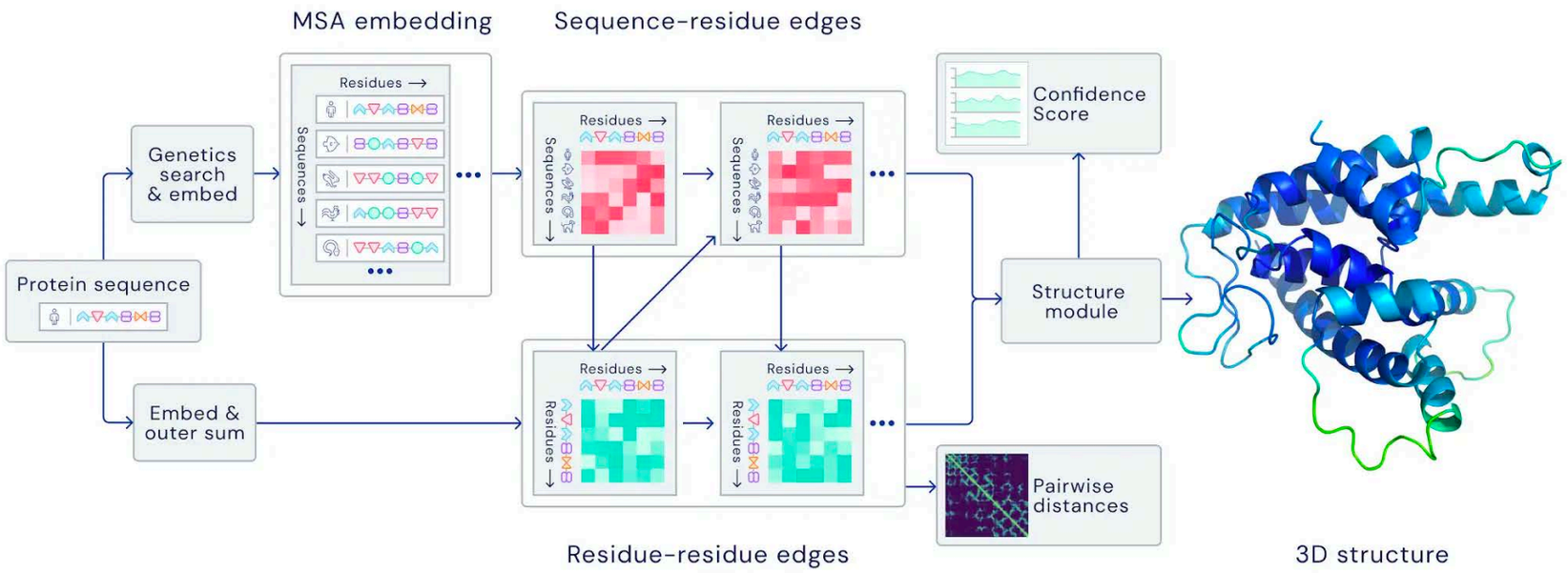
Future: Alphafold and beyond



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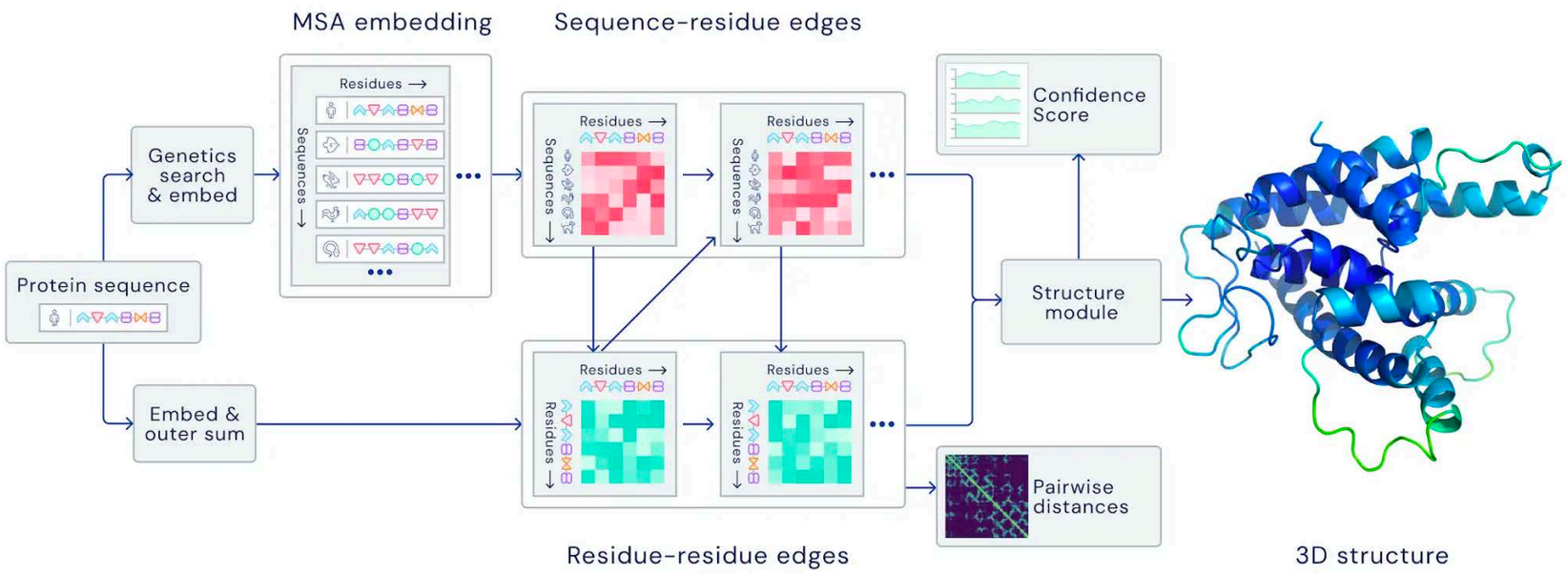

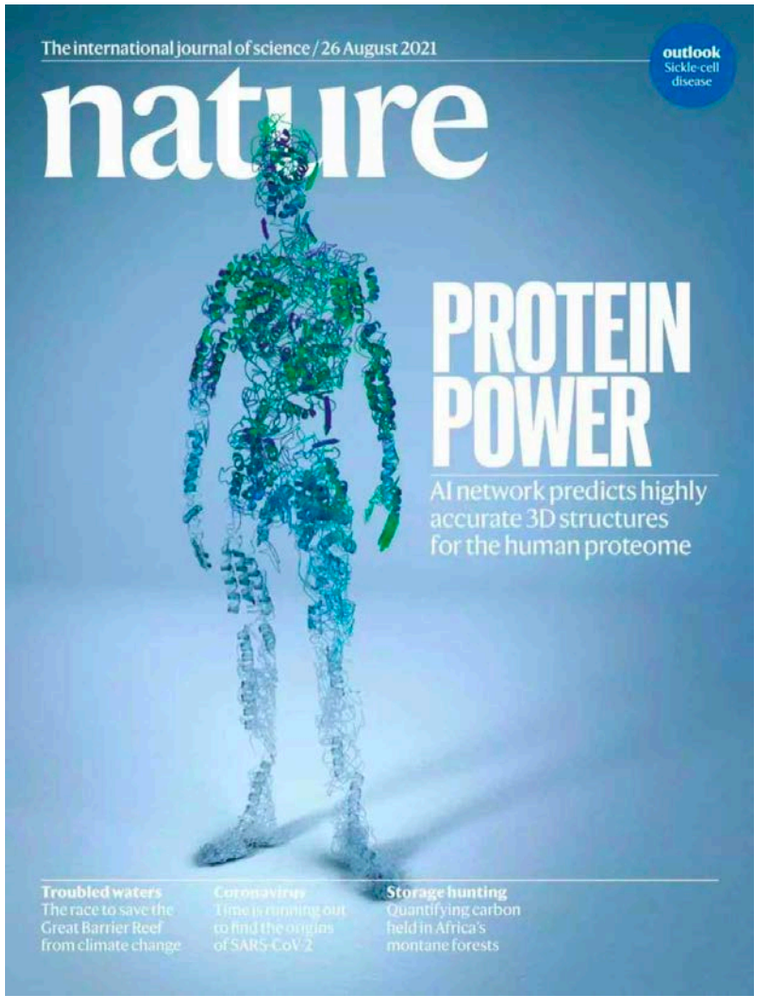

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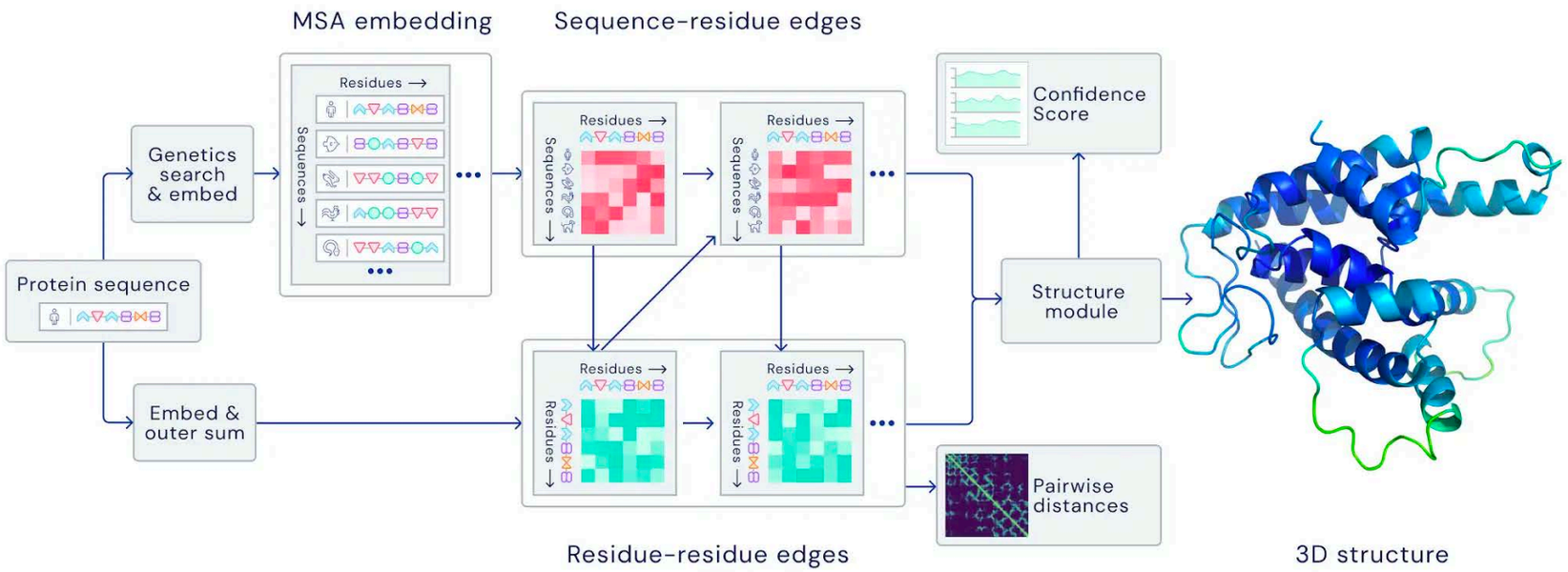

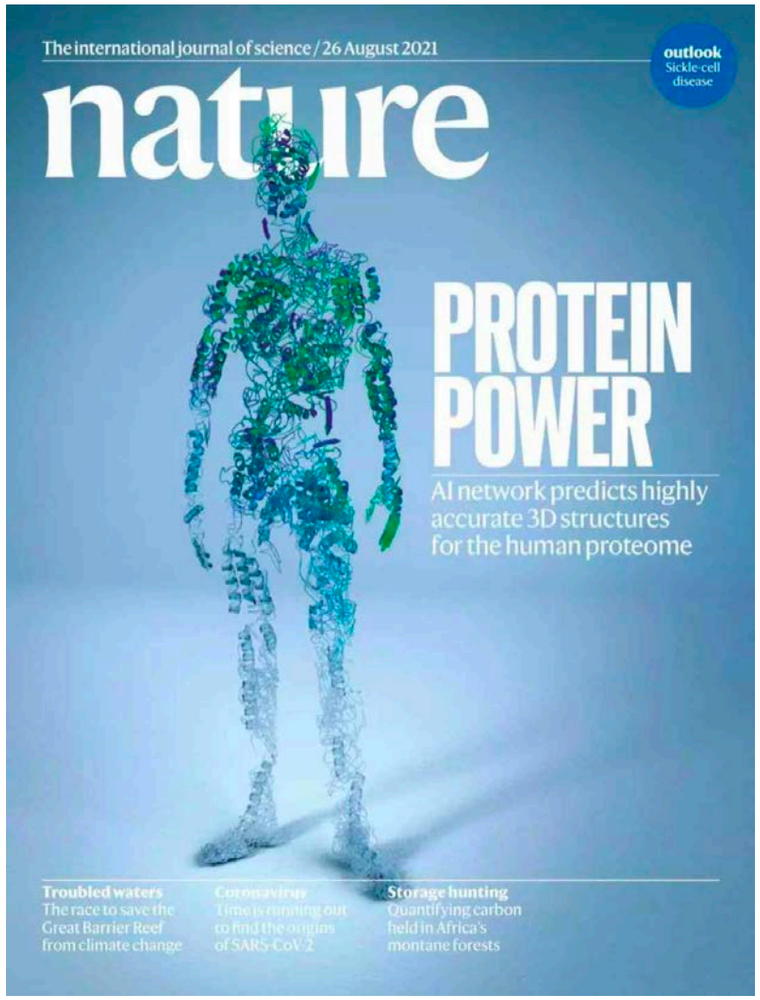

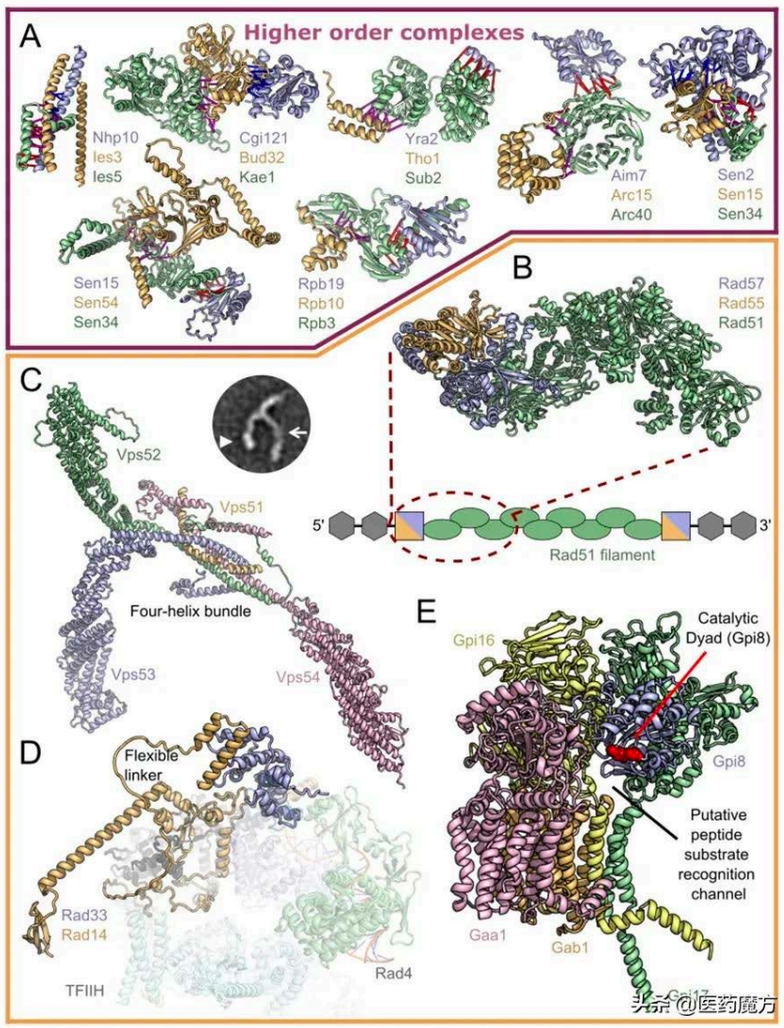

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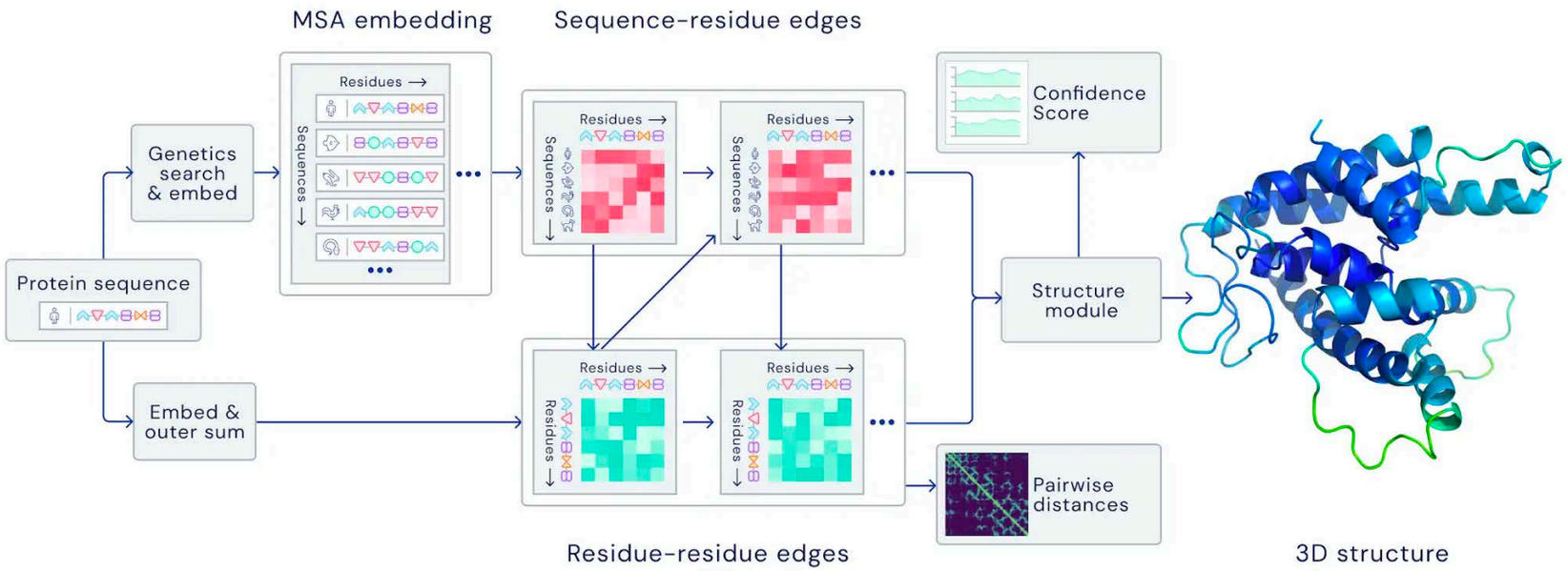

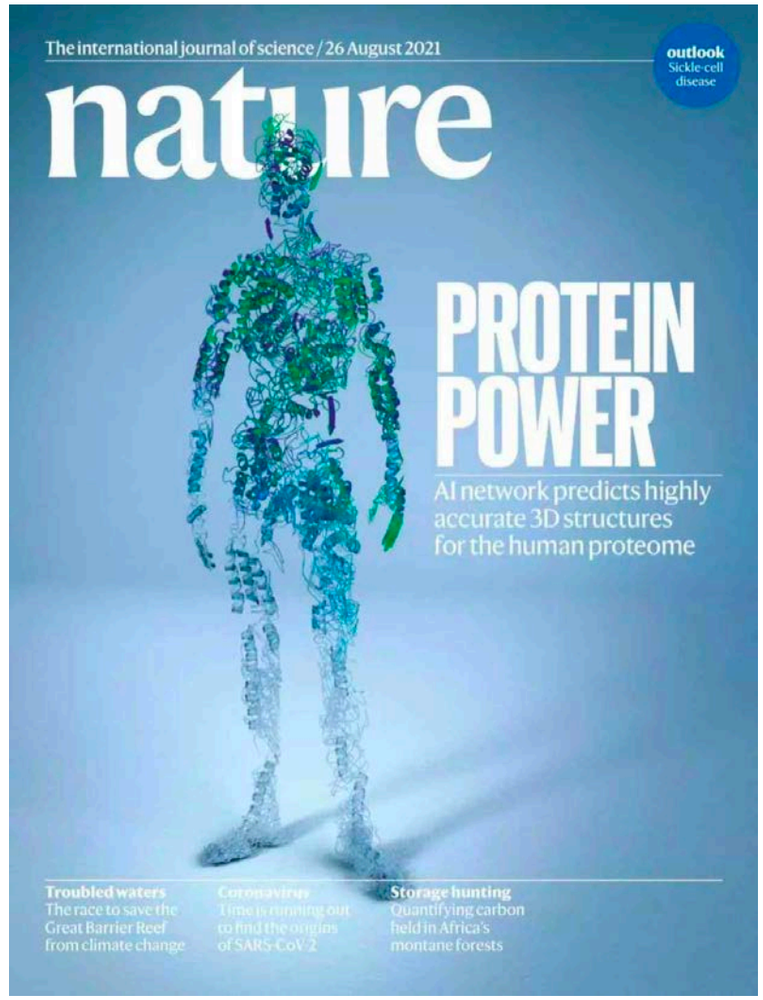

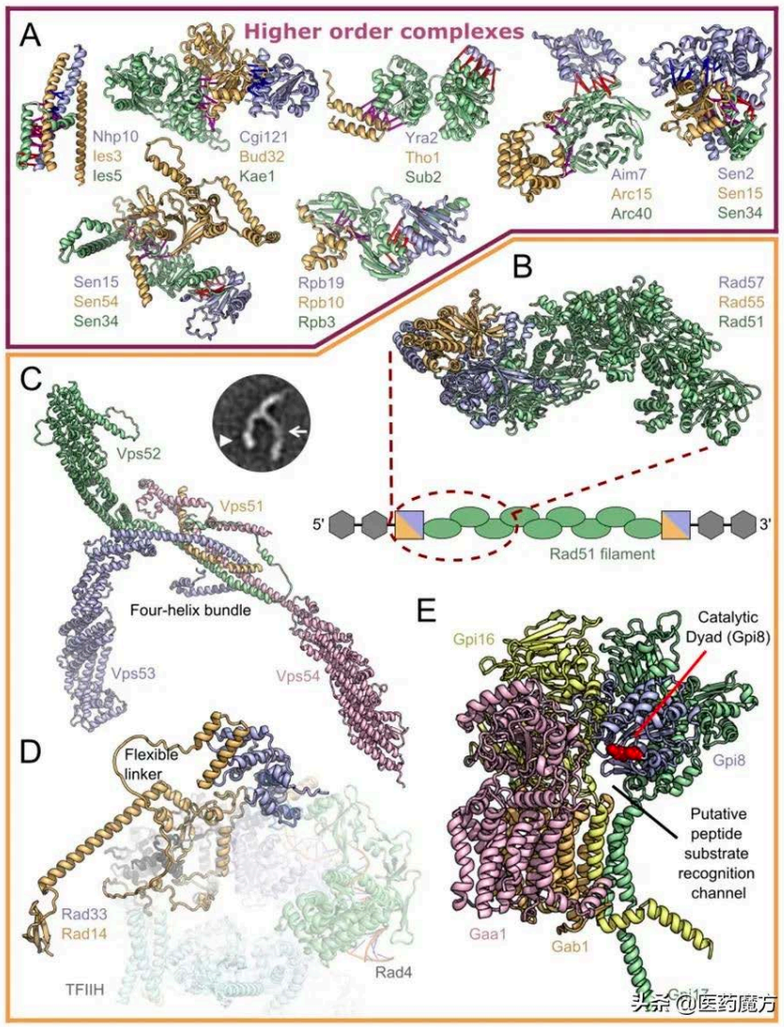

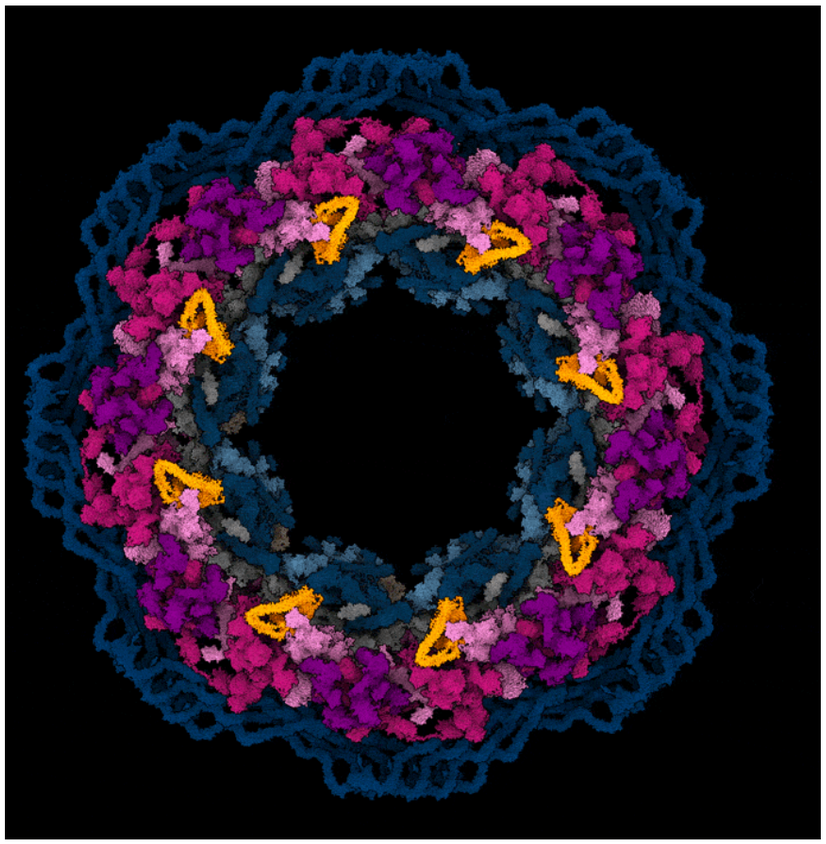

Mosalaganti et al, bioRxiv, 2021

Ahmad Reza Mehdipour

Future: More possibilities

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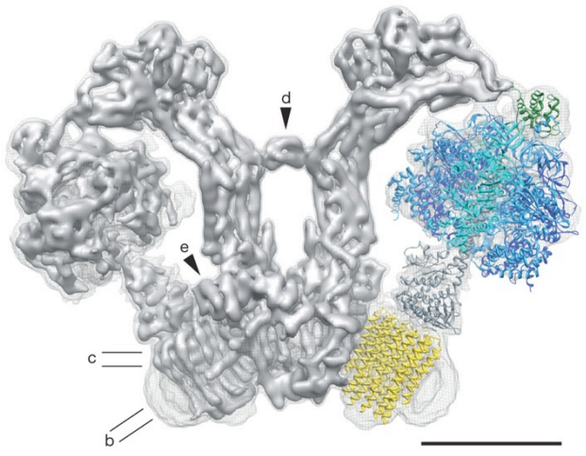
Future: More possibilities

Cryo-electron-microscopy



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Future: More possibilities

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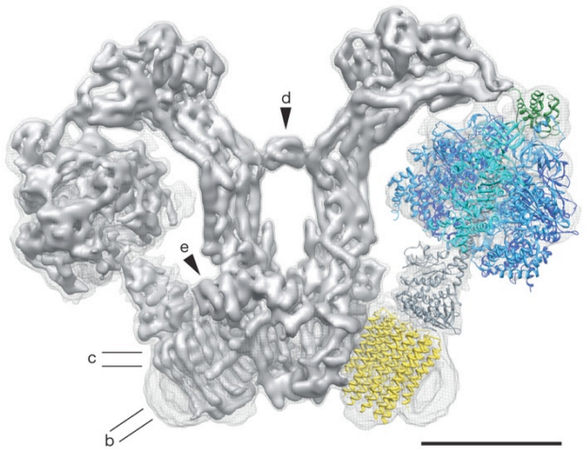
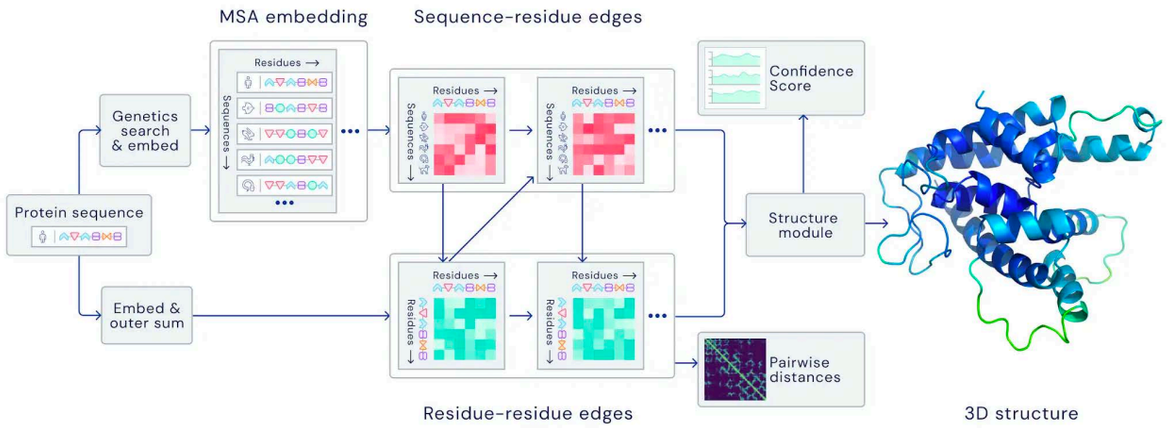


Alphafold



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Future: More possibilities

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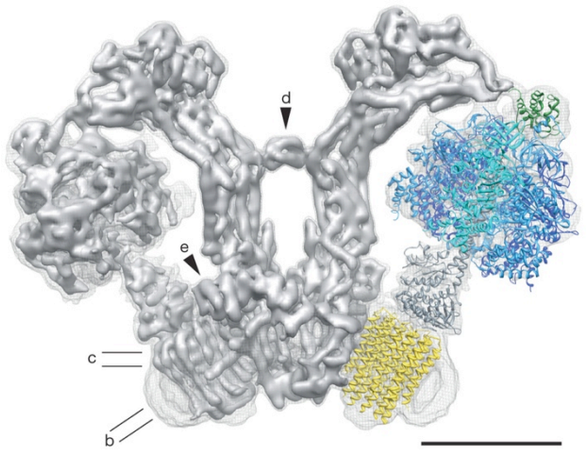

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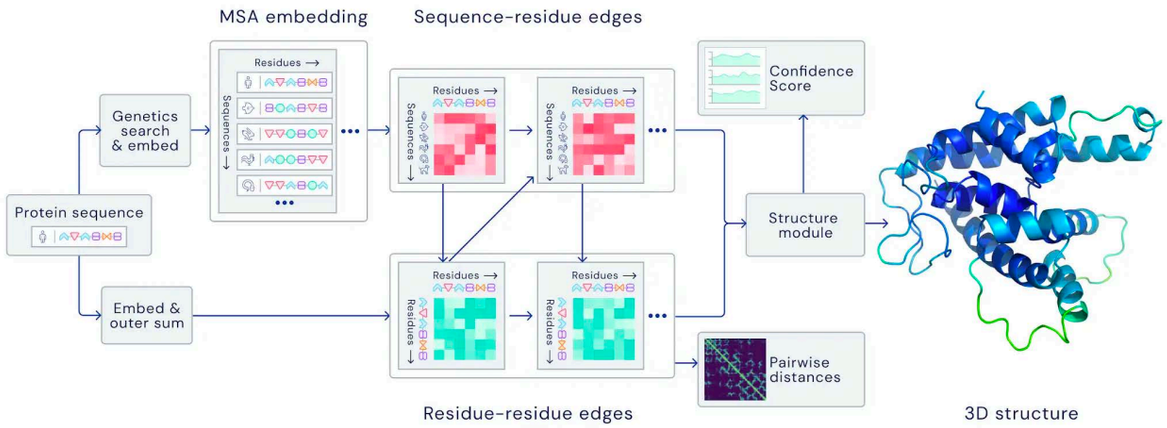
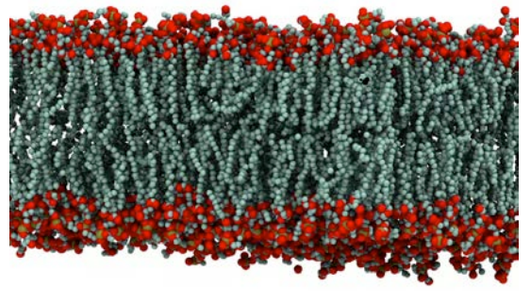


MD simulations



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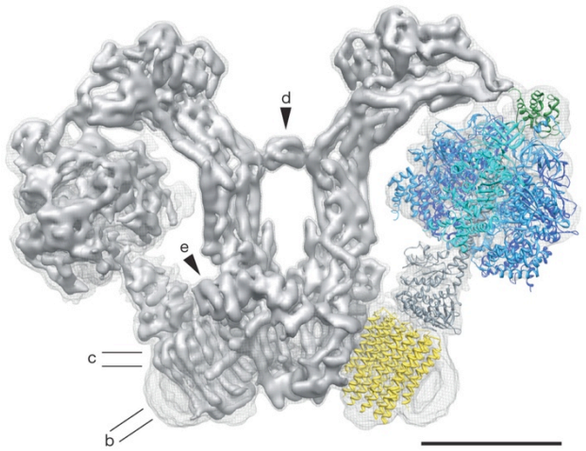
Future: More possibilities

Cryo-electron-microscopy



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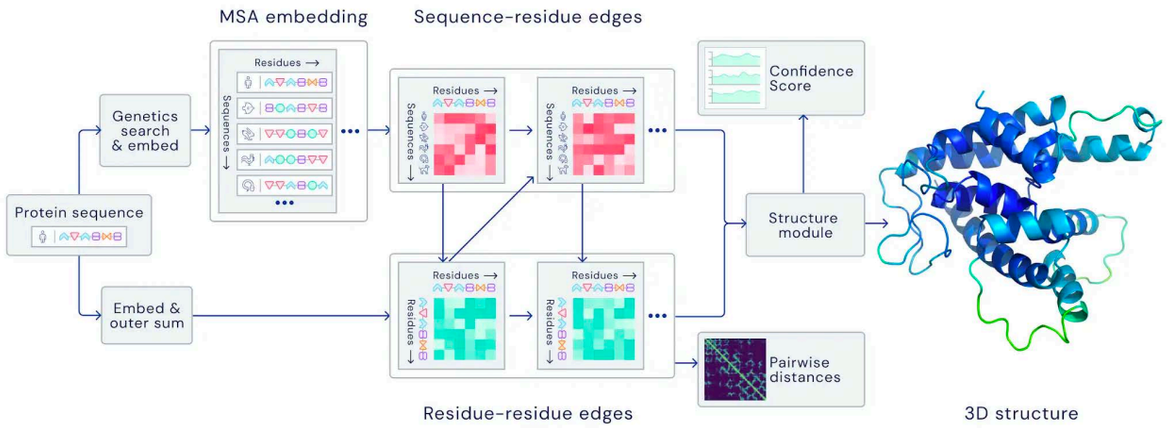
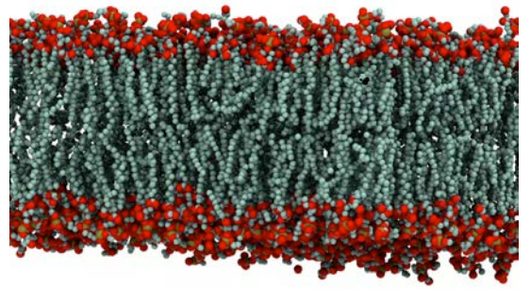


MD simulations



Future: More possibilities

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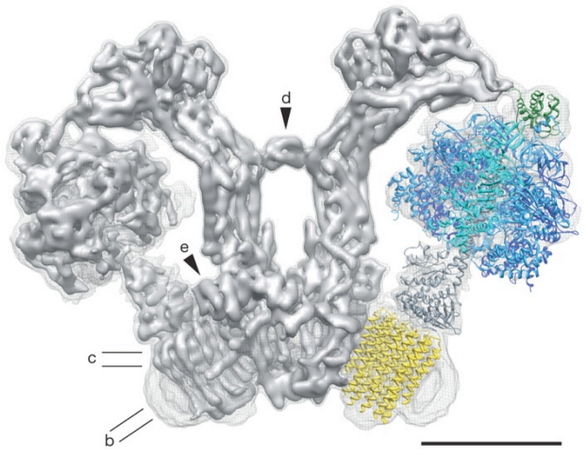
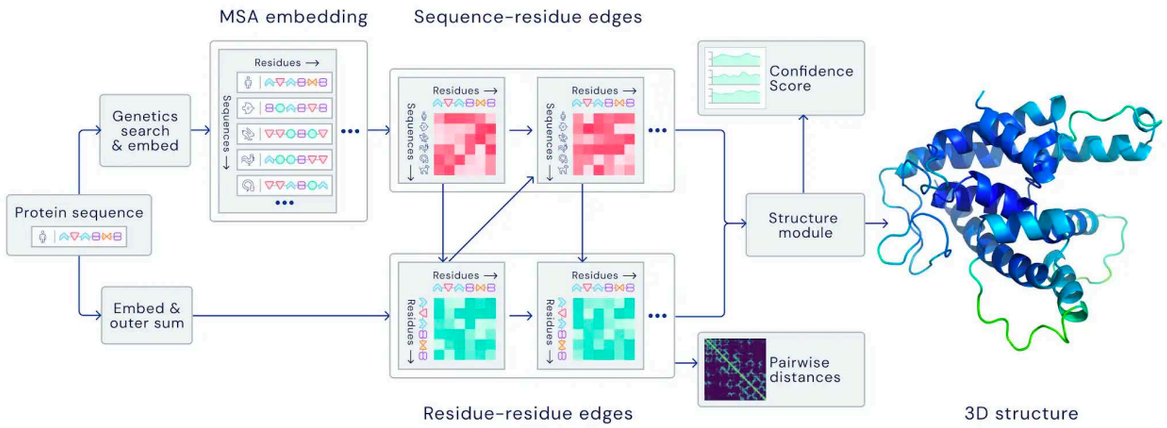
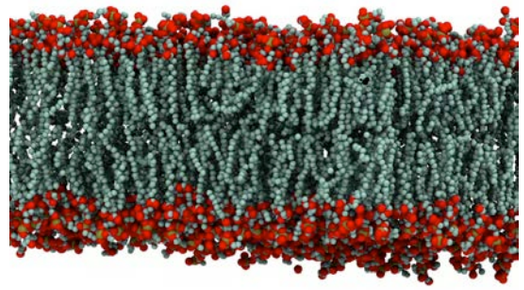
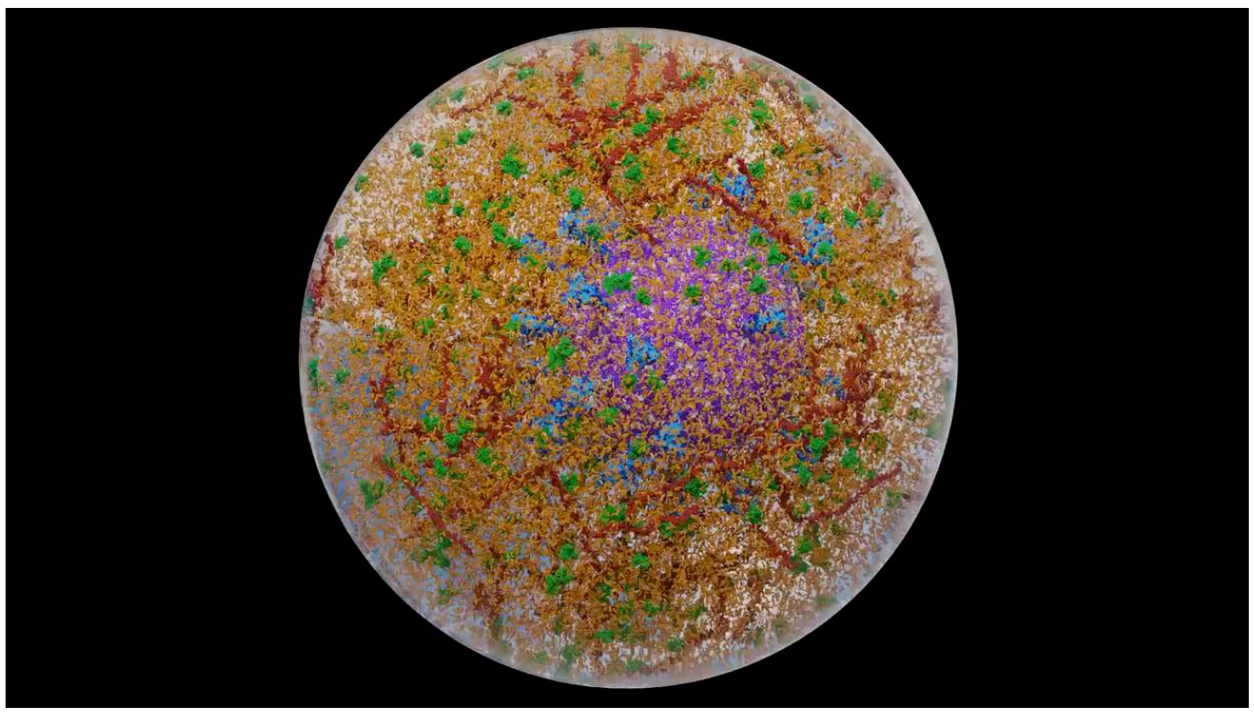


Alphafold



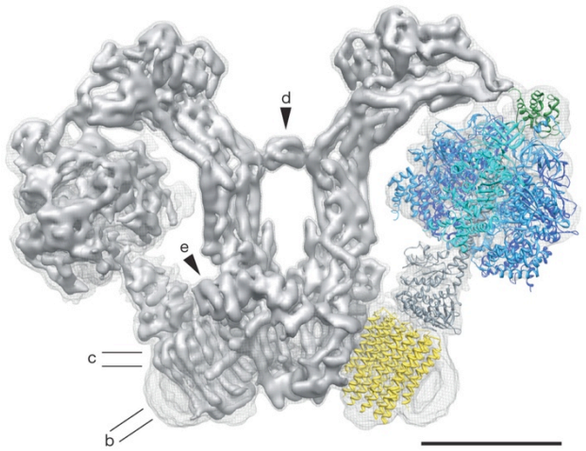
MD simulations





Future: More possibilities

Cryo-electron-microscopy



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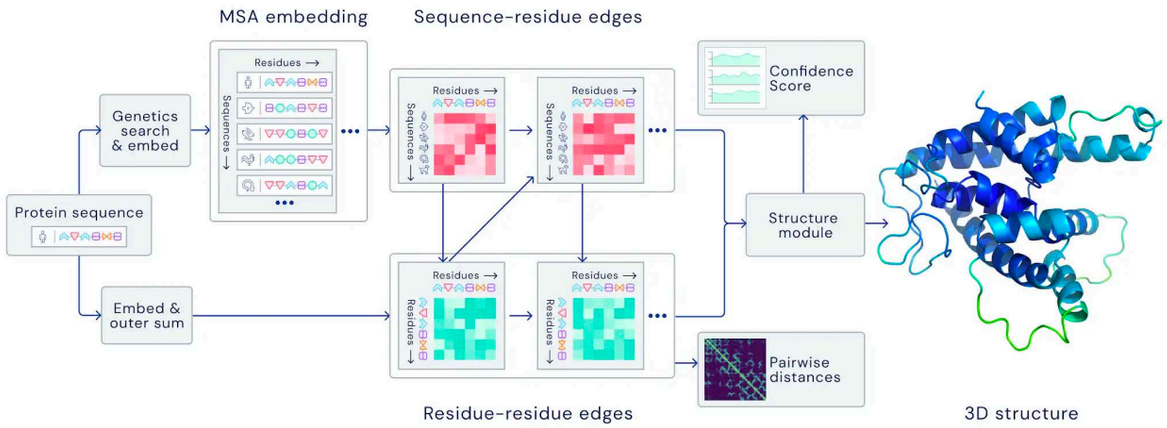
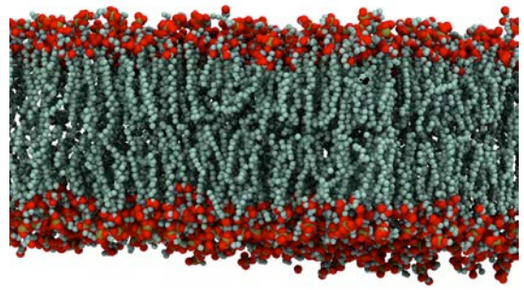
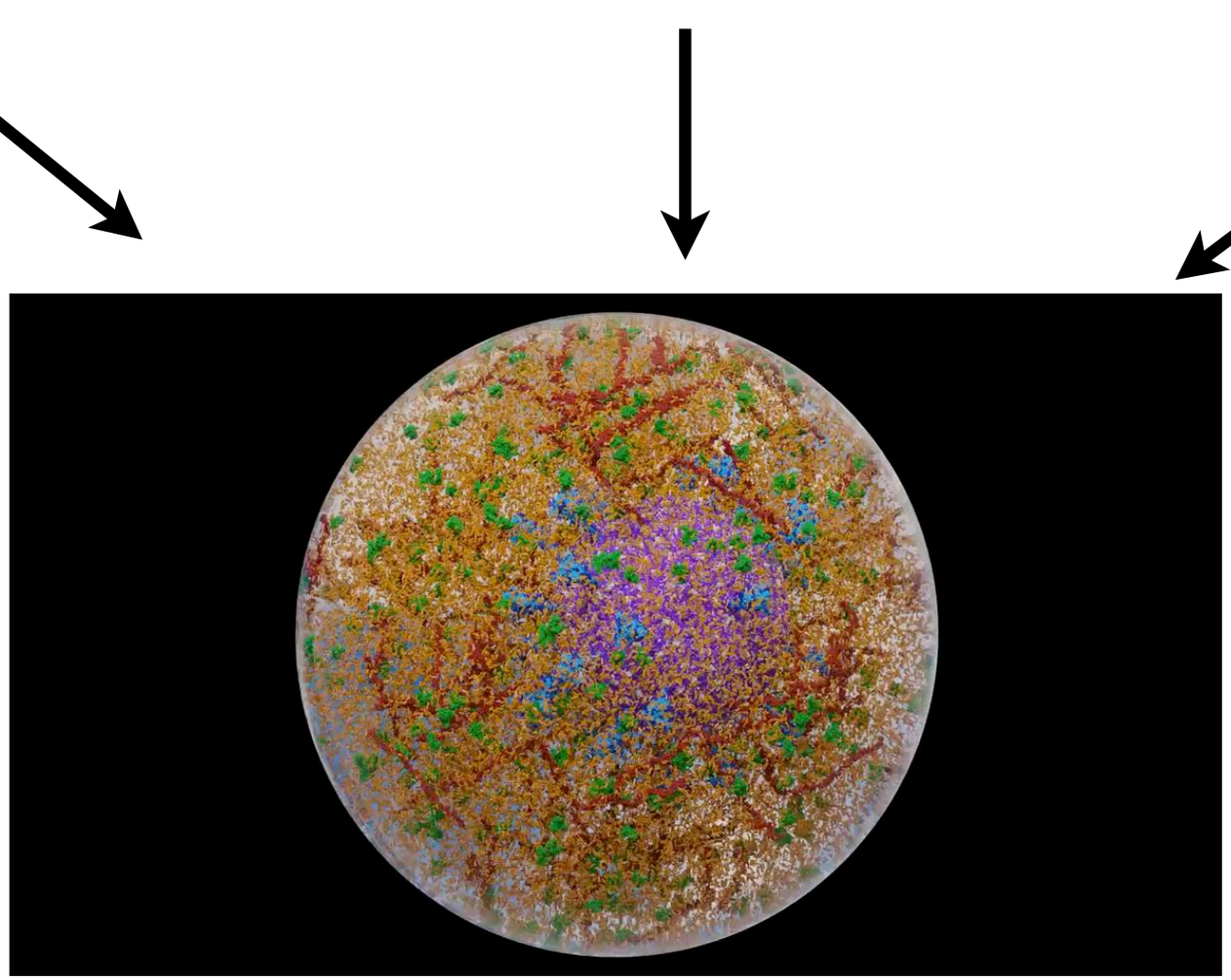


MD simulations





Simulation of an aerosol drop containing SARS-CoV2 virus

Total number of atoms: 1.3 billion atoms

Simulation time: 1 μs

Rommie Amaro Lab, New York Times, 2021

CENTER FOR MOLECULAR MODELING

Thank you!

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